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NEWS 4	Apr 09	ZDB will be removed from STN
NEWS 5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 9	Jun 03	New e-mail delivery for search results now available
NEWS 10	Jun 10	MEDLINE Reload
NEWS 11	Jun 10	PCTFULL has been reloaded
NEWS 12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 15	Jul 30	NETFIRST to be removed from STN
NEWS 16	Aug 08	CANCERLIT reload
NEWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18	Aug 08	NTIS has been reloaded and enhanced
NEWS 19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 23	Sep 03	JAPIO has been reloaded and enhanced
NEWS 24	Sep 16	Experimental properties added to the REGISTRY file
NEWS 25	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 26	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 27	Oct 21	EVENTLINE has been reloaded
NEWS 28	Oct 24	BEILSTEIN adds new search fields
NEWS 29	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 30	Oct 25	MEDLINE SDI run of October 8, 2002
NEWS 31	Nov 18	DKILIT has been renamed APOLLIT
NEWS 32	Nov 25	More calculated properties added to REGISTRY
NEWS 33	Dec 02	TIBKAT will be removed from STN
NEWS 34	Dec 04	CSA files on STN
NEWS 35	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 36	Dec 17	TOXCENTER enhanced with additional content
NEWS 37	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 38	Dec 30	ISMEC no longer available
NEWS 39	Jan 13	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS 40	Jan 21	NUTRACEUT offering one free connect hour in February 2003
NEWS 41	Jan 21	PHARMAML offering one free connect hour in February 2003
NEWS 42	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 43	Feb 13	CANCERLIT is no longer being updated
NEWS 44	Feb 24	METADEX enhancements

NEWS 45 Feb 24 PCTGEN now available on STN
NEWS 46 Feb 24 TEMA now available on STN
NEWS 47 Feb 26 NTIS now allows simultaneous left and right truncation
NEWS 48 Feb 26 PCTFULL now contains images
NEWS 49 Mar 04 SDI PACKAGE for monthly delivery of multifile SDI results

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=> s GLAT derivative
L1 0 GLAT DERIVATIVE

=> s glatiramer acetate
L2 748 GLATIRAMER ACETATE

=> s l2 and copolymer 1
L3 257 L2 AND COPOLYMER 1

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L4 5 L3 AND DERIVATIVE

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L5 1 DUP REMOVE L4 (4 DUPLICATES REMOVED)

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L5 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
2001299797 Document Number: 20415838. PubMed ID: 10961665.
Glatiramer acetate (**copolymer-1**
)-specific, human T cell lines: cytokine profile and suppression of T cell lines reactive against myelin basic protein. Dabbert D; Rosner S; Kramer M; Scholl U; Tumani H; Mader M; Weber F. (Department of Neurology, Georg-August-University, Gottingen, Germany.) NEUROSCIENCE LETTERS, (2000 Aug 11) 289 (3) 205-8. Journal code: 7600130. ISSN: 0304-3940. Pub. country: Ireland. Language: English.
AB **Glatiramer acetate** (GA), represents an established treatment of relapsing/remitting multiple sclerosis (MS). The mechanisms responsible for the effect of GA are not fully understood. We generated GA-, myelin basic protein (MBP)- and purified protein **derivative** (PPD)-specific T cell lines from three MS patients and one healthy donor. The GA-specific lines were CD3+, CD4+, CD8- and produced tumor-necrosis-factor-alpha (TNF-alpha), interferon-gamma (IFN-gamma), interleukin-4 (IL-4), interleukin-6 (IL-6) and interleukin-10 (IL-10) after stimulation with GA in the presence of irradiated peripheral blood mononuclear cells. MBP-specific T cell lines showed an identical phenotype and secreted TNF-alpha, IFN-gamma, IL-4, IL-10, but not IL-6. Co-culture experiments demonstrated, that GA-specific T cell lines have the capability to suppress the proliferation of MBP-specific T cell lines.

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L6 515 L2 AND TREATMENT

=> s l6 and autoimmune
L7 128 L6 AND AUTOIMMUNE

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3 FILES SEARCHED...
L8 0 L7 AND T CELL MEDIATED

=> s l7 and rheumatoid arthritis
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L10 3 DUP REMOVE L9 (0 DUPLICATES REMOVED)

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L10 ANSWER 1 OF 3 SCISEARCH COPYRIGHT 2003 ISI (R)
2002:825012 The Genuine Article (R) Number: 600GG. **Treatment** of multiple sclerosis with the pregnancy hormone estriol. Sicotte N L; Liva S M; Klutch R; Pfeiffer P; Bouvier S; Odesa S; Wu T C J; Voskuhl R R (Reprint). Univ Calif Los Angeles, Reed Neurol Res Ctr, Dept Neurol, 710 Westwood Plaza, Los Angeles, CA 90095 USA (Reprint); Univ Calif Los Angeles, Reed Neurol Res Ctr, Dept Neurol, Los Angeles, CA 90095 USA; Univ Calif Los Angeles, Hlth Sci Ctr, Dept Obstet & Gynecol, Los Angeles, CA 90095 USA. ANNALS OF NEUROLOGY (OCT 2002) Vol. 52, No. 4, pp. 421-428. Publisher: WILEY-LISS. DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012 USA. ISSN: 0364-5134. Pub. country: USA. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB Multiple sclerosis patients who become pregnant experience a

significant decrease in relapses that may be mediated by a shift in immune responses from T helper I to T,helper 2. Animal models of multiple sclerosis have shown that the pregnancy hormone, estriol, can ameliorate disease and can cause an immune shift. We treated nonpregnant female multiple sclerosis patients with the pregnancy hormone estriol in an attempt to recapitulate the beneficial effect of pregnancy. As compared with pretreatment baseline, relapsing remitting patients treated with oral estriol (8mg/day) demonstrated significant decreases in delayed type hypersensitivity responses to tetanus, interferon-gamma levels in peripheral blood mononuclear cells, and gadolinium enhancing lesion numbers and volumes on monthly cerebral magnetic resonance images. When estriol **treatment** was stopped, enhancing lesions increased to pretreatment levels. When estriol. **treatment** was reinstituted, enhancing lesions again were significantly decreased. Based on these results, a larger, placebo-controlled trial of estriol is warranted in women with relapsing remitting multiple sclerosis. This novel **treatment** strategy of using pregnancy doses of estriol in multiple sclerosis has relevance to other **autoimmune** diseases that also improve during pregnancy.

L10 ANSWER 2 OF 3 SCISEARCH COPYRIGHT 2003 ISI (R)
2002:323406 The Genuine Article (R) Number: 537PX. **Treatment** of multiple sclerosis with cyclophosphamide: critical review of clinical and immunologic effects. Weiner H L (Reprint); Cohen J A. Brigham & Womens Hosp, Ctr Neurol Dis, 77 Ave Louis Pasteur, HIM 730, Boston, MA 02115 USA (Reprint); Harvard Univ, Sch Med, Brigham & Womens Hosp, Massachusetts Gen Hosp, Multiple Sclerosis Ctr, Boston, MA 02115 USA; Cleveland Clin Fdn, Mellen Ctr U10, Cleveland, OH 44195 USA. MULTIPLE SCLEROSIS (APR 2002) Vol. 8, No. 2, pp. 142-154. Publisher: ARNOLD, HODDER HEADLINE PLC. 338 EUSTON ROAD, LONDON NW1 3BH, ENGLAND. ISSN: 1352-4585. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Cyclophosphamide is an alkylating agent used to treat malignancies and immune-mediated inflammatory non-malignant processes such as lupus nephritis and immune-mediated neuropathies. It has been studied as a **treatment** for multiple sclerosis (MS) for the post 30 years and is used by physicians in selected cases of progressive or worsening MS. Review of published reports suggests that it is efficacious in cases of worsening MS that have an inflammatory component as evidenced by relapses and/or gadolinium (Gd)-enhancing lesions on magnetic resonance imaging (MRI) or in patients in earlier stages of disease where inflammation predominates over degenerative processes in the central nervous system (CNS). There is no evidence of efficacy in primary progressive MS or later stages of secondary progressive MS. Although a general immunosuppressant that affects both T- and B-cell function, cyclophosphamide has selective immune effects in MS by suppressing IL-12 and Th1-type responses and enhancing Th2/Th3 responses (IL-4, IL-10, TGF-beta; eosinophils in peripheral blood). Side effects include nausea, alopecia, infertility, bladder toxicity and risk of malignancy. The most commonly used regimens involve every 4- to 8-week outpatient IV pulse therapy given with or without corticosteroids and are usually well-tolerated by patients. Cyclophosphamide is currently used in patients whose disease is not controlled by beta-interferon or **glatiramer acetate** and those with rapidly worsening MS.

L10 ANSWER 3 OF 3 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2003:113391 Document No.: PREV200300113391. Immunotherapy of multiple sclerosis: Where are we? Where should we go. Martin, Roland (1); Stuerzebecher, Claus-Steffen; McFarland, Henry F. (1). (1) Neuroimmunology Branch, NINDS, National Institutes of Health, 10 Center DR, Building 10, Room 5B-16, MSC 1400, Bethesda, MD, 20892-1400, USA: martinr@ninds.nih.gov USA. Nature Immunology, (September 2001, 2001) Vol. 2, No. 9, pp. 785-788. print. ISSN: 1529-2908. Language: English.

AB Differences in multiple sclerosis patient's disease and their responses to standard drugs indicate that today's therapies need to be more individualized. It is proposed that gene expression profiling in conjunction with magnetic resonance imaging be used to optimize future **treatment** approaches.

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L11 45 L7 AND INFLAMMATORY

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L12 20 DUP REMOVE L11 (25 DUPLICATES REMOVED)

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L12 ANSWER 1 OF 20 MEDLINE DUPLICATE 1
2003071203 Document Number: 22469139. PubMed ID: 12581542. A comparison of the mechanisms of action of interferon beta and **glatiramer acetate** in the **treatment** of multiple sclerosis. Zhang Jingwu; Hutton George; Zang Ying. (Department of Neurology, Baylor College of Medicine, Houston, Texas 77030, USA.. jzang@bcm.tmc.edu) . CLINICAL THERAPEUTICS, (2002 Dec) 24 (12) 1998-2021. Journal code: 7706726. ISSN: 0149-2918. Pub. country: United States. Language: English.
AB BACKGROUND: The development of immunomodulatory agents has represented a major advance in the **treatment** of multiple sclerosis (MS). To date, immunomodulatory agents approved for the **treatment** of relapsing MS in the United States include 3 forms of recombinant interferon (IFN) beta (2 formulations of IFN beta-1a and 1 of IFN beta-1b) and synthetic **glatiramer acetate** (GA). Recognition of how these agents work to regulate the immune system may lead to a better understanding of disease mechanisms, as well as to development of more effective therapies or combinations of therapy. OBJECTIVE: This article reviews the potential mechanisms of action of IFN beta products and GA in the context of their regulatory effects on **autoimmune** components that may be of importance in MS. METHODS: MEDLINE and Current Contents/Clinical Medicine were searched for articles published in English from 1993 to the present using the search terms interferon beta, **glatiramer acetate**, and multiple sclerosis. RESULTS: IFN beta products affect the disease process in MS through multiple potential mechanisms of action, including antiviral, antiproliferative, and anti-**inflammatory** effects. The mechanisms of action of GA are less clear, but may involve immune regulation induced by a gradual shift of T-cell phenotype from proinflammatory (type 1 T-helper cells) to anti-**inflammatory** (type 2 T-helper cells) and interference with antigen presentation. CONCLUSION: Understanding the mechanisms of action of IFN beta products and GA provides important insights into the disease processes involved in MS.

L12 ANSWER 2 OF 20 SCISEARCH COPYRIGHT 2003 ISI (R)
2002:799312 The Genuine Article (R) Number: 596JH. Differential mechanisms of action of interferon-beta and **glatiramer acetate** in MS
. Yong V W (Reprint). Univ Calgary, Dept Oncol, 3330 Hosp Dr, Calgary, AB T2N 4N1, Canada (Reprint); Univ Calgary, Dept Oncol, Calgary, AB T2N 4N1, Canada; Univ Calgary, Dept Clin Neurosci, Calgary, AB T2N 4N1, Canada. NEUROLOGY (24 SEP 2002) Vol. 59, No. 6, pp. 802-808. Publisher: LIPPINCOTT WILLIAMS & WILKINS. 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA. ISSN: 0028-3878. Pub. country: Canada. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Interferon-beta and **glatiramer acetate** (GA) are the two main groups of drugs used in the **treatment** of MS. Notably, while both ultimately decrease CNS inflammation, they do so by very different mechanisms. Interferon-beta has potent activity at the

blood-brain barrier and impairs the trafficking of **inflammatory** cells into the CNS. In contrast, GA has negligible effect at the blood-brain barrier, allowing GA-specific T helper 2 lymphocytes to enter the CNS to decrease inflammation through bystander suppression. Other differences are also emphasized. The presence of GA-reactive lymphocytes within the CNS parenchyma may have the additional benefit of conferring neuroprotection through protective autoimmunity.

L12 ANSWER 3 OF 20 SCISEARCH COPYRIGHT 2003 ISI (R)
2002:505133 The Genuine Article (R) Number: 560GT. Anti-**inflammatory** strategies to prevent axonal injury in multiple sclerosis. Rieckmann P (Reprint); Maurer M. Univ Wurzburg, Dept Neurol, Clin Res Unit Multiple Sclerosis & Neuroimmunol, Josef Schneider Str 11, D-97080 Wurzburg, Germany (Reprint); Univ Wurzburg, Dept Neurol, Clin Res Unit Multiple Sclerosis & Neuroimmunol, D-97080 Wurzburg, Germany. CURRENT OPINION IN NEUROLOGY (JUN 2002) Vol. 15, No. 3, pp. 361-370. Publisher: LIPPINCOTT WILLIAMS & WILKINS. 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA. ISSN: 1350-7540. Pub. country: Germany. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Axonal injury in multiple sclerosis has attracted considerable interest during the past few years. It has been demonstrated in association with inflammation within active lesions, but it is also present in normal-appearing white matter. Because axonal loss appears to be responsible for persistent neurological deficits in patients with multiple sclerosis, **treatment** strategies to prevent damage to neurites and restore function are of paramount importance in controlling the disease process. Some of the currently available immunomodulatory therapies may also reduce axonal damage, as demonstrated using improved imaging technologies, but the precise mechanisms that could protect axons during the **inflammatory** attack are yet to be identified. Factors that are involved in functional impairment of axonal conduction and those elements that are responsible for direct structural damage to the axon are both potential targets for therapeutic interventions.

L12 ANSWER 4 OF 20 MEDLINE DUPLICATE 2
2002370515 Document Number: 22111371. PubMed ID: 12114110. Dual action of **glatiramer acetate** (Cop-1) in the **treatment** of CNS **autoimmune** and neurodegenerative disorders. Kipnis Jonathan; Schwartz Michal. (Dept of Neurobiology, The Weizmann Institute of Science, 76100 Rehovot, Israel.) Trends Mol Med, (2002 Jul) 8 (7) 319-23. Ref: 64. Journal code: 100966035. ISSN: 1471-4914. Pub. country: England: United Kingdom. Language: English.
AB Protective autoimmunity is the body's defense mechanism against destructive self-compounds such as those commonly associated with neurodegenerative disorders. **Autoimmune** disease and neurodegenerative disorders can thus be viewed as two extreme manifestations of the same process. Therefore, when designing therapy, it is important to avoid an approach that will cure the one by invoking the other. One way to stop, or at least slow down, the progression of neurodegeneration without risking development of an **autoimmune** disease is by boosting protective autoimmunity in a well-controlled way. Copolymer 1 (Cop-1), an approved drug for the **treatment** of multiple sclerosis, can be used as a **treatment** for **autoimmune** diseases and as a therapeutic vaccine for neurodegenerative diseases. We propose that the protective effect of Cop-1 vaccination is obtained through a well-controlled **inflammatory** reaction, and that the activity of Cop-1 in driving this reaction derives from its ability to serve as a 'universal antigen' by weakly activating a wide spectrum of self-reactive T cells.

L12 ANSWER 5 OF 20 SCISEARCH COPYRIGHT 2003 ISI (R)
2002:600857 The Genuine Article (R) Number: 572XM. Cytokine production in T lymphocyte-microglia interaction is attenuated by **glatiramer**

CENTORIAN DR, PRIVATE BAG 65901, MAIRANGI BAY, AUCKLAND 10, NEW ZEALAND.
ISSN: 1173-8804. Pub. country: Germany. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The therapy for multiple sclerosis (MS) has changed dramatically over the past decade. Recent immunobiological findings and current pathophysiological concepts together with advances in biotechnology, improvements in clinical trial design and development of magnetic resonance imaging have led to a variety of evaluable therapeutic approaches in MS. However, in contrast to the successfully introduced and established immunomodulatory therapies (e.g. interferon-beta and **glatiramer acetate**), there have been a remarkable number of therapeutic failures as well. Despite convincing immunological concepts, impressive data from animal models and promising results from phase I/II studies, the drugs and strategies investigated showed no benefit or even turned out to have unexpectedly severe adverse effects.

Although to date there is no uniformly accepted model for MS, there is agreement on the significance of **inflammatory** events mediated by autoreactive T cells in the CNS. These can be modified therapeutically at the individual steps of a hypothetical pathogenetic cascade. Crucial corners like: (i) the prevalence and peripheral activation of CNS-autoreactive T cells in the periphery; (ii) adhesion and penetration of T cells into the CNS; (iii) local activation and proliferation and; (iv) de- and remyelination processes can be targeted through their putative mediators. Like a 'specificity pyramid', therapeutic approaches therefore cover from general immunosuppression up to specific targeting of T-cell receptor peptide major histocompatibility (MHC) complex.

We discuss in detail clinical MS trials that failed or were discontinued for other reasons. These trials include cytokine modulators [tumour necrosis factor (TNF)-alpha antagonists, interleukin-10, interleukin-4, transforming growth factor-beta2], immunosuppressive agents (roquininex, gusperimus, sulfasalazine, cladribine), inducers of remyelination [intravenous immunoglobulins (IVIg)], antigen-derived therapies [oral tolerance, altered peptide ligands (APL), MHC-Peptide blockade], T cell and T-cell receptor directed therapies (T cell vaccination, T-cell receptor peptide vaccination), monoclonal antibodies against leucocyte differentiation molecules (anti-CD3, anti-CD4), and inactivation of circulating T cells (extracorporeal photopheresis).

The main conclusions that can be drawn from these 'negative' experiences Lire as follows. Theoretically promising agents may paradoxically increase disease activity (lenercept, inflixiniab), be associated with unforeseen adverse effects (e.g. roquinimex) or short-term favourable trends may reverse with prolonged follow-up (e.g. sulfasalzine). One should not be too enthusiastic about successful trials in animal models (TNFalpha blockers; oral tolerance; remyelinating effect of IVIg) nor be irritated by non-scientific media hype (deoxyspergualine; bone marrow transplantation). More selectivity can imply less efficacy (APL, superselective interventions like T-cell receptor vaccination) and antigen-related therapies can stimulate rather than inhibit encephalitogenic cells. Failed strategies are of high importance for a critical revision of assumed immunopathological mechanisms, their neuroimaging correlates, and for future trial design. Since failed trials add to our growing understanding of multiple sclerosis, 'misses' are nearly as important to the scientific process as the 'hits'.

L12 ANSWER 8 OF 20 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 4
2002328715 EMBASE Prospects for therapeutic vaccination with **glatiramer acetate** for neurodegenerative diseases such as Alzheimer's disease. Schwartz M.; Kipnis J.. M. Schwartz, Department of Neurobiology, Weizmann Institute of Science, Rehovot 76100, Israel. michal.schwartz@weizmann.ac.il. Drug Development Research 56/2 (143-149) 2002.
Refs: 64.
ISSN: 0272-4391. CODEN: DDREDK. Pub. Country: United States. Language:

acetate: a mechanism for therapeutic efficacy in multiple sclerosis. Chabot S; Yong F P; Le D M; Metz L M; Myles T; Yong V W (Reprint). Univ Calgary, Neurosci Res Grp, Fac Med, Dept Clin Neurosci, 3330 Hosp Dr NW, Calgary, AB T2N 4N1, Canada (Reprint); Univ Calgary, Neurosci Res Grp, Fac Med, Dept Clin Neurosci, Calgary, AB T2N 4N1, Canada; Univ Calgary, Fac Med, Dept Oncol, Calgary, AB T2N 4N1, Canada. MULTIPLE SCLEROSIS (AUG 2002) Vol. 8, No. 4, pp. 299-306. Publisher: ARNOLD, HODDER HEADLINE PLC. 338 EUSTON ROAD, LONDON NW1 3BH, ENGLAND. ISSN: 1352-4585. Pub. country: Canada. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The efficacy of **glatiramer acetate** in multiple sclerosis (MS) is thought to involve the production of Th2 regulatory lymphocytes that secrete anti-**inflammatory** cytokines, however, other mechanisms cannot be excluded. Given that activated T lymphocytes infiltrate into the CNS and become in close proximity to microglia, we evaluated whether **glatiramer acetate** affects the potential interaction between T cells and microglia. We report that the co-culture of activated T lymphocytes with microglia led to the induction of several cytokines, and that these were reduced by **glatiramer acetate treatment**. Morphological transformation of bipolar/ramified microglia into an activated ameboid form was attenuated by **glatiramer acetate**. These results reveal a novel mechanism for **glatiramer acetate**: the impairment of activated T cells to effectively interact with microglia to produce cytokines. The net result of a non-**inflammatory** milieu within the CNS, in spite of T cell infiltration, may help account for the amelioration of disease activity in MS patients on **glatiramer acetate** therapy.

L12 ANSWER 6 OF 20 MEDLINE DUPLICATE 3
2002147407 Document Number: 21676149. PubMed ID: 11818475. Multiple sclerosis. Keegan B Mark; Noseworthy John H. (Department of Neurology, Mayo Clinic and Mayo Foundation, 200 First Street SW, Rochester, Minnesota 55905, USA.) ANNUAL REVIEW OF MEDICINE, (2002) 53 285-302. Ref: 95. Journal code: 2985151R. ISSN: 0066-4219. Pub. country: United States. Language: English.

AB Multiple sclerosis (MS) is a common **inflammatory** disease of the central nervous system (CNS). Diagnosis rests upon identifying typical clinical symptoms and interpreting supportive laboratory and radiological investigations. The etiology is unknown; however, strong evidence suggests that MS is an **autoimmune** disease directed against CNS myelin or oligodendrocytes. Genetic factors are important in the development of MS. Contributing environmental determinants (possibly including infectious agents) appear important but remain unidentified. Both cell-mediated and humorally mediated immune mechanisms contribute to pathological injury. Axonal damage occurs in addition to demyelination and may be the cause of later permanent disability. Distinct pathological subtypes may differentiate among patients with MS. **Treatment** is directed at acute attacks (with corticosteroids) and reduction of attack frequency (primarily with type-1 beta interferons and **glatiramer acetate**). Research into the causes and **treatments** of MS has expanded our knowledge of this disease and promises improved care for MS patients in the future.

L12 ANSWER 7 OF 20 SCISEARCH COPYRIGHT 2003 ISI (R)
2002:665235 The Genuine Article (R) Number: 581HH. Therapeutic approaches in multiple sclerosis - Lessons from failed and interrupted **treatment** trials. Wiendl H (Reprint); Hohlfeld R. Univ Tubingen, Sch Med, Dept Neurol, Hoppe Seyler Str 3, D-72076 Tubingen, Germany (Reprint); Univ Tubingen, Sch Med, Dept Neurol, D-72076 Tubingen, Germany; Klinikum Grosshadern, Inst Clin Neuroimmunol, Munich, Germany; Max Planck Inst Neurobiol, Dept Neuroimmunol, Martinsried, Germany. BIODRUGS (JUL 2002) Vol. 16, No. 3, pp. 183-200. Publisher: ADIS INTERNATIONAL LTD. 41

English. Summary Language: English.

AB Neurodegenerative diseases, whatever their primary causes, are characterized by certain common features, one of which is their self-perpetuating nature. The ongoing progression of the disorder is due to the effects of destructive self-compounds, whose presence in the tissues is an outcome of the early phase of the disease and which gradually destroy remaining functional neurons. Studies in our laboratory have led to the recent formulation of a novel concept of protective autoimmunity as the body's mechanism of defense against these destructive self-compounds. This **autoimmune** response to central nervous system (CNS) insults is mediated by T-cells and presumably operates by activating and regulating local microglia and infiltrating macrophages (**inflammatory** response) to carry out their function of clearing destructive material from the tissue at risk. We suggest that a well-controlled autoimmunity counteracts and overcomes the destructive effects of the potentially harmful self-compounds, at the cost of some loss of tissue. An additional risk to the individual is the induction of an **autoimmune** disease, which is likely to occur if the **autoimmune** response is malfunctioning. An optimal balance of the various factors will lead to an outcome of maximal benefit at minimal cost to the tissue. A procedure for safely boosting the **autoimmune** response, by vaccination with a weak self-crossreactive antigen such as **glatiramer acetate** (also known as Cop-1) was found to protect rats from glutamate toxicity, a major mediator of the spread of damage and a well-known causative factor in neurodegenerative disorders. Cop-1, when administered according to a different regimen, is an FDA-approved drug for the **treatment** of multiple sclerosis. Different formulations of the same drug can therefore be used to treat two extreme manifestations of chronic degenerative diseases of the CNS.

L12 ANSWER 9 OF 20 MEDLINE DUPLICATE 5

2002251629 Document Number: 21986268. PubMed ID: 11990872.

Treatment of multiple sclerosis with cyclophosphamide: critical review of clinical and immunologic effects. Weiner H L; Cohen J A. (Multiple Sclerosis Center, Brigham and Women's Hospital, Massachusetts General Hospital, Harvard Medical School, Boston 02115, USA.. hweiner@rics.bwh.harvard.edu) . MULTIPLE SCLEROSIS, (2002 Apr) 8 (2) 142-54. Ref: 95. Journal code: 9509185. ISSN: 1352-4585. Pub. country: England: United Kingdom. Language: English.

AB Cyclophosphamide is an alkylating agent used to treat malignancies and immune-mediated **inflammatory** non-malignant processes such as lupus nephritis and immune-mediated neuropathies. It has been studied as a **treatment** for multiple sclerosis (MS) for the past 30 years and is used by physicians in selected cases of progressive or worsening MS. Review of published reports suggests that it is efficacious in cases of worsening MS that have an **inflammatory** component as evidenced by relapses and/or gadolinium (Gd)-enhancing lesions on magnetic resonance imaging (MRI) or in patients in earlier stages of disease where inflammation predominates over degenerative processes in the central nervous system (CNS). There is no evidence of efficacy in primary progressive MS or later stages of secondary progressive MS. Although a general immunosuppressant that affects both T- and B-cell function, cyclophosphamide has selective immune effects in MS by suppressing IL-12 and Th1-type responses and enhancing Th2/Th3 responses (IL-4, IL-10, TGF-beta; eosinophils in peripheral blood). Side effects include nausea, alopecia, infertility, bladder toxicity and risk of malignancy. The most commonly used regimens involve every 4- to 8-week outpatient i.v. pulse therapy given with or without corticosteroids and are usually well-tolerated by patients. Cyclophosphamide is currently used in patients whose disease is not controlled by beta-interferon or **glatiramer acetate** and those with rapidly worsening MS.

L12 ANSWER 10 OF 20 SCISEARCH COPYRIGHT 2003 ISI (R)
2002:746597 The Genuine Article (R) Number: 589PJ. Sustained immunological effects of **Glatiramer acetate** in patients with multiple sclerosis treated for over 6 years. Chen M; Conway K; Johnson K P; Martin R; Dhib-Jalbut S (Reprint). Univ Maryland Hosp, Dept Neurol, Rm N4W46, 22 S Greene St, Baltimore, MD 21201 USA (Reprint); Univ Maryland, Sch Med, Baltimore, MD 21201 USA; NINDS, Neuroimmunol Branch, NIH, Bethesda, MD 20892 USA; Baltimore VA Med Ctr, Baltimore, MD 21201 USA. JOURNAL OF THE NEUROLOGICAL SCIENCES (15 SEP 2002) Vol. 201, No. 1-2, pp. 71-77. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0022-510X. Pub. country: USA. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB The availability of a group of multiple sclerosis (MS) patients at the University of Maryland, who had participated in the pivotal Copaxones trial in the early 1990s, provided an opportunity to examine the long-term immunologic effects of **Glatiramer acetate** (GA) **treatment** in MS. Forty-eight GA-reactive T-cell lines (TCL) were generated from 10 MS patients who have been receiving GA **treatment** for 6-9 years. Proliferative responses, cytokine production, and cross-reactivity with myelin basic protein (MBP) and the MBP immunodominant peptide 83-99 were compared to responses obtained from 10 MS patients who were tested pretreatment and after a shorter period of **treatment** ranging from 1 to 10 months. The results indicate that while long-term **treatment** with GA results in a 2.9-fold decrease in the estimated precursor frequency of GA-reactive T-cells, the sustained response to GA remains Th2-biased and in part cross-reactive with MBP and MBP (83-99) as measured by proliferation and cytokine release assays. The results indicate that despite a drop in the precursor frequency of GA-reactive T-cells with long-term **treatment**, the sustained response remains predominantly Th2-biased and cross-reactive with MBP, which is consistent with the anti-**inflammatory** effects of the drug and bystander suppression. (C) 2002 Elsevier Science B.V. All rights reserved.

L12 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2003 ACS
2001:903779 Document No. 136:687 The use of **glatiramer acetate** (copolymer 1) in the **treatment** of central nervous system disorders. Young, V. Wee; Chabot, Sophie (Teva Pharmaceuticals Industries, Ltd., Can.; Teva Pharmaceuticals USA). PCT Int. Appl. WO 2001093828 A1 20011213, 76 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US18248 20010605. PRIORITY: US 2000-587523 20000605.

AB The present invention involves the administration of Copolymer 1 (**glatiramer acetate**) to treat **inflammatory**, non-**autoimmune** central nervous system (CNS) diseases, alleviate the symptoms thereof, inhibit the activity of matrix metalloproteinases and suppress cytokine prodn. by T lymphocytes.

L12 ANSWER 12 OF 20 SCISEARCH COPYRIGHT 2003 ISI (R)
2001:897964 The Genuine Article (R) Number: 490EA. Expression of urokinase plasminogen activator receptor on monocytes from patients with relapsing-remitting multiple sclerosis: Effect of **glatiramer acetate** (Copolymer 1). Balabanov R; Lisak D; Beaumont T; Lisak R P; Dore-Duffy P (Reprint). Wayne State Univ, Sch Med, Detroit Med Ctr, Dept Neurol, Div Neuroimmunol, Multiple Sclerosis Clin Res Ctr, 421 E Canfield, 3124 Elliman, Detroit, MI 48201 USA (Reprint); Wayne State Univ,

Sch Med, Detroit Med Ctr, Dept Neurol, Div Neuroimmunol, Multiple Sclerosis Clin Res Ctr, Detroit, MI 48201 USA; Univ Chicago Hosp, Dept Neurol, Chicago, IL 60637 USA. CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY (NOV 2001) Vol. 8, No. 6, pp. 1196-1203. Publisher: AMER SOC MICROBIOLOGY. 1752 N ST NW, WASHINGTON, DC 20036-2904 USA. ISSN: 1071-412X . Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Multiple sclerosis (MS) is a chronic **inflammatory** disease of the central nervous system in which peripheral blood monocytes play an important role. We have previously reported that patients with chronic progressive MS (CPMS) have significantly increased numbers of circulating monocytes which express the urokinase plasminogen activator receptor (uPAR). In the present study, we examined the expression of uPAR on monocytes in patients with relapsing-remitting multiple sclerosis (RRMS) not currently participating in a clinical trial and in patients with RRMS who were enrolled in a double-blind multicenter clinical trial designed to examine the effect of **glatiramer acetate** (copolymer 1; Copaxone) on relapsing disease. Patients with CPMS have sustained high levels of circulating uPAR-positive (uPAR(+)) monocytes. In comparison, patients with RRMS displayed variable levels of circulating uPAR(+) monocytes. Mean values for uPAR in patients with RRMS were above those seen for controls but were not as high as those observed for patients with secondary progressive MS. Patients with RRMS in the clinical trial also had variable levels of monocyte uPAR. However, patients in the **treatment** group displayed lower levels following 2 years of **treatment**. In both placebo-treated and **glatiramer acetate**-treated patients, the percentage of circulating uPAR(+) monocytes, as well as the density of uPAR expressed per cell (mean linear fluorescence intensity), increased just prior to the onset of a clinically documented exacerbation. Values fell dramatically with the development of clinical symptoms. uPAR levels in all groups correlated with both clinical activity and severity. Results indicate that monocyte activation is impatient in MS and that **glatiramer acetate** may have a significant effect on monocyte activation in patients with RRMS.

L12 ANSWER 13 OF 20 SCISEARCH COPYRIGHT 2003 ISI (R)
2001:694986 The Genuine Article (R) Number: 465QD. **Glatiramer acetate** induces a Th2-biased response and crossreactivity with myelin basic protein in patients with MS. Chen M; Gran B; Costello K; Johnson K; Martin R; Dhib-Jalbut S (Reprint). Univ Maryland Hosp, Dept Neurol, Rm N4W46, 22 S Greene St, Baltimore, MD 21201 USA (Reprint); Univ Maryland, Sch Med, Baltimore, MD 21201 USA; NINDS, Neuroimmunol Branch, NIH, Bethesda, MD 20892 USA; Baltimore VA Med Ctr, Baltimore, MD 21201 USA . MULTIPLE SCLEROSIS (AUG 2001) Vol. 7, No. 4, pp. 209-219. Publisher: ARNOLD, HODDER HEADLINE PLC. 338 EUSTON ROAD, LONDON NW1 3BH, ENGLAND. ISSN: 1352-4585. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Glatiramer acetate** (GA) is an approved **treatment** for multiple sclerosis (MS). The proposed mechanism of action is the induction of GA-specific T cells characterized by protective anti-**inflammatory** Th2 response. We tested this hypothesis in II MS patients treated with GA from 1 - 19 months. Interferon-gamma and IL-5 (markers of Th1 and Th2 responses respectively) were assayed by ELISA in GA-specific T-cell lines (TCL) supernatants. Th1/Th2 bias was defined based on the ratio of IFN-gamma /IL-5 secretion. Fifty-eight pre-**treatment** and 75 on-**treatment** GA-specific TCL were generated. On-**treatment** mean IL-5 levels in GA-TCL increased significantly, whereas those for IFN-gamma were markedly reduced. Consequently, the ratio of IFN gamma /IL-5 also shifted in favor of a Th2 response. The percentage of GA-TCL classified as Th I was decreased, whereas those classified as TH increased on-**treatment** as compared to pre-**treatment**. Some GA-specific TC (approximately 25%) generated during **treatment** secreted predominantly IL-5 in

response to MBP and the immunodominant MBP peptide 83-99, indicating that these crossreactive antigens can act as partial agonists for GA-reactive TCL. These results strongly suggest that the mechanism of action of GA in MS involves the induction of crossreactive GA-specific T cells with a predominant Th2 cytokine profile.

L12 ANSWER 14 OF 20 MEDLINE DUPLICATE 6
2001447183 Document Number: 21126505. PubMed ID: 11223159.
Glatiramer acetate blocks interleukin-1-dependent nuclear factor-kappaB activation and RANTES expression in human U-251 MG astroglial cells. Li Q Q; Bever C T. (Departments of Neurology, University of Maryland School of Medicine, 21201, Baltimore, MD, USA.. qli001@umaryland.edu) . BRAIN RESEARCH. MOLECULAR BRAIN RESEARCH, (2001 Feb 19) 87 (1) 48-60. Journal code: 8908640. ISSN: 0169-328X. Pub. country: Netherlands. Language: English.
AB RANTES is a basic 8-kDa polypeptide of the C-C chemokine subfamily with strong chemoattractant activity for T lymphocytes and monocytes/macrophages that are implicated in the pathogenesis of multiple sclerosis (MS) lesions. **Glatiramer acetate** is a drug recently approved for the **treatment** of MS. We therefore investigated the effect of **glatiramer acetate** on RANTES expression in glial cells in vitro. **Treatment** of human U-251 MG astroglial cells with **glatiramer acetate** blocks IL-1beta-induced RANTES chemokine production in a dose- and time-dependent manner. **Glatiramer acetate** also decreased steady-state levels of RANTES mRNA in these cells, which was attributable to reduced transcription, as assessed by nuclear run-on assays. In addition, we showed that NF-kappaB may be the transcriptional activator responsible for the IL-1beta-mediated RANTES gene expression in this system. Our data indicated that the IL-1beta-induced increase in RANTES was associated with an increase in in vitro nuclear extract binding activity specific for the NF-kappaB site in the promoter region of the RANTES gene. The increases in RANTES mRNA and protein expression were suppressed by the NF-kappaB inhibitors gliotoxin, isohelenin, and pyrrolidine dithiocarbamate (PDTC). Furthermore, we demonstrated that the increase in NF-kappaB DNA-binding activity was prevented by pretreatment with **glatiramer acetate** or the NF-kappaB inhibitors. Our results suggest that **glatiramer acetate** may inhibit IL-1beta-stimulated RANTES expression in human glial cells by blocking NF-kappaB activation, thus identifying part of the molecular basis for its anti-**inflammatory** and immunosuppressive effects in demyelinating diseases.

L12 ANSWER 15 OF 20 MEDLINE DUPLICATE 7
2001557175 Document Number: 21489669. PubMed ID: 11603112. [New approaches in research of therapy of multiple sclerosis]. Neue Forschungsansatze zur Therapie der multiplen Sklerose. Hemmer B; Cepok S; Nessler S; Sommer N. (Arbeitsgruppe fur klinische Neuroimmunologie, Neurologische Klinik, Philipps-Universitat Marburg.. hemmer@mailer.uni-marburg.de) . MEDIZINISCHE KLINIK, (2001 Sep 15) 96 Suppl 1 23-8. Journal code: 8303501. ISSN: 0723-5003. Pub. country: Germany: Germany, Federal Republic of. Language: German.
AB BACKGROUND: Multiple sclerosis is a chronic **inflammatory** demyelinating disease of the central nervous system. With a prevalence of 0.1-0.15% in Germany multiple sclerosis is the most common cause of severe disability in young adults. PATHOGENESIS: Epidemiological and family studies demonstrate the role of environmental and genetic factors in the pathogenesis of multiple sclerosis. Based on those observations and findings in experimental animal models, it is believed that multiple sclerosis is caused by an **autoimmune** process. However, target antigens and mechanisms leading to tissue destruction are largely unknown. THERAPY: Since the efficacy of current immunomodulatory and immunosuppressive therapies (beta-interferons, **glatiramer**

acetate, mitoxantrone) is limited, it is necessary to develop new strategies for the **treatment** of multiple sclerosis. To reach this goal, a much better understanding of disease pathogenesis is necessary which takes into account the clinical, paraclincial and histopathological heterogeneity of the disease. CONCLUSION: Only further intensive research activity on basic mechanisms of disease pathogenesis and a consequent development of resulting therapeutic strategies--from animal models to phase III studies--will result in significant improvement of the long-term course of multiple sclerosis.

L12 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2003 ACS
2000:34733 Document No. 132:88184 Inhibitors of the interaction of glutamate with the AMPA and/or kainate receptor complex for **treatment** of demyelinating disorders. Turski, Lechoslaw; Smith, Terence (Eisai Co., Ltd, Japan). PCT Int. Appl. WO 2000001376 A2 20000113, 104 pp. DESIGNATED STATES: W: JP, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB2112 19990702. PRIORITY: GB 1998-14380 19980702; GB 1998-24393 19981106.

AB New therapies can be devised based upon a demonstration of the role of glutamate in the pathogenesis of demyelinating disorders. Inhibitors of the interaction of glutamate with the AMPA and/or kainate receptor complex are likely to be useful in treating demyelinating disorders and can be formulated as pharmaceutical compns.

L12 ANSWER 17 OF 20 MEDLINE DUPLICATE 8
2001022672 Document Number: 20481932. PubMed ID: 11027347. Specific Th2 cells accumulate in the central nervous system of mice protected against experimental **autoimmune** encephalomyelitis by copolymer 1. Aharoni R; Teitelbaum D; Leitner O; Meshorer A; Sela M; Arnon R. (Departments of Immunology and Biological Services, The Weizmann Institute of Science, Rehovot 76100, Israel.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 Oct 10) 97 (21) 11472-7. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB This study addresses the issue of the effect of immunomodulating therapies in the target organ-the central nervous system (CNS)-in the case of multiple sclerosis. Copolymer 1 (Cop 1, Copaxone, **glatiramer acetate**), an approved drug for the **treatment** of multiple sclerosis, is a potent inducer of Th2 regulatory cells in both mice and humans. Highly reactive Cop 1-specific T cell lines that secrete IL-4, IL-5, IL-6, IL-10, and transforming growth factor-beta in response to Cop 1 and crossreact with myelin basic protein (MBP) at the level of Th2 cytokine secretion were established from both brains and spinal cords of Cop 1-treated mice. In contrast, no reactivity to the control antigen lysozyme could be obtained in lymphocytes isolated from CNS of mice injected with lysozyme. Adoptively transferred labeled Cop 1-specific suppressor cells were found in brain sections 7 and 10 days after their injection to the periphery, whereas lysozyme-specific cells were absent in the CNS. Hence, Cop 1-induced Th2 cells cross the blood-brain barrier and accumulate in the CNS, where they can be stimulated in situ by MBP and thereby exert therapeutic effects in the diseased organ. This therapeutic effect was manifested, in brains of experimental **autoimmune** encephalomyelitis-induced mice, by a decrease in the **inflammatory** cytokine interferon-gamma and by secretion of the anti-**inflammatory** cytokine IL-10 in response to the autoantigen MBP.

L12 ANSWER 18 OF 20 MEDLINE DUPLICATE 9
1999199272 Document Number: 99199272. PubMed ID: 10097125. Immunomodulation of experimental **autoimmune** encephalomyelitis by oral administration of copolymer 1. Teitelbaum D; Arnon R; Sela M. (Department of Immunology, Weizmann Institute of Science, Rehovot, Israel 76100, USA.. Liteitel@Weizmann.Weizmann.ac.il) . PROCEEDINGS OF THE

NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Mar 30) 96 (7) 3842-7. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The activity of copolymer 1 (Cop 1, Copaxone, **glatiramer acetate**) in suppressing experimental **autoimmune** encephalomyelitis (EAE) and in the **treatment** of multiple sclerosis patients when injected parenterally has been extensively demonstrated. In the present study we addressed the question of whether Cop 1 can induce oral tolerance to EAE similar to myelin basic protein (MBP). We now have demonstrated that oral Cop 1 inhibited EAE induction in both rats and mice. Furthermore, oral Cop 1 was more effective than oral MBP in suppressing EAE in rats. The beneficial effect of oral Cop 1 was found to be associated with specific inhibition of the proliferative and Th1 cytokine secretion responses to MBP of spleen cells from Cop 1-fed mice and rats. In all of these assays, oral Cop 1 was more effective than oral MBP. The tolerance induced by Cop 1 could be adoptively transferred with spleen cells from Cop 1-fed animals. Furthermore, Cop 1-specific T cell lines, which inhibit EAE induction in vivo, could be isolated from the above spleen cells. These T cell lines secrete the anti-**inflammatory** cytokines IL-10 and transforming growth factor type beta, but not IL-4, in response to both Cop 1 and MBP. In conclusion, oral Cop 1 has a beneficial effect on the development of EAE that is associated with down-regulation of T cell immune responses to MBP and is mediated by Th2/3 type regulatory cells. These results suggest that oral administration of Cop 1 may modulate multiple sclerosis as well.

L12 ANSWER 19 OF 20 MEDLINE

1999080668 Document Number: 99080668. PubMed ID: 9863300. [**Treatment** of multiple sclerosis--1. New drugs may be effective but there still are frequent relapses]. Behandling av multipel skleros--1. Nya lakemedel ger lindring vid tata skov. Svenningsson A; Andersson M; Olsson T. (Neurologiska kliniken, Karolinska sjukhuset, Stockholm.) LAKARTIDNINGEN, (1998 Dec 2) 95 (49) 5623-7, 5630. Ref: 19. Journal code: 0027707. ISSN: 0023-7205. Pub. country: Sweden. Language: Swedish.

AB Multiple sclerosis (MS) is a demyelinating, central nervous system disease, of putative **autoimmune** pathogenesis. Although no effective pharmacological therapy has been available for this often disabling disease until recently, several studies have now confirmed that subcutaneous or intramuscular administration of beta-interferon may reduce the frequency and severity of relapses in relapsing MS, and may also inhibit disease progression. Studies are under way to determine the possible efficacy of beta-interferon during the progressive phase of the disease. Three beta-interferon formulations are currently available in Sweden. Another drug, **glatiramer acetate**, also shown to have some effect on the disease course, is expected to be registered for use in Sweden shortly.

L12 ANSWER 20 OF 20 SCISEARCH COPYRIGHT 2003 ISI (R)

1999:64413 The Genuine Article (R) Number: 155KJ. **Treatment** of multiple sclerosis with Copolymer-1 (Copaxone(R)): implicating mechanisms of Th1 to Th2/Th3 immune-deviation. Miller A (Reprint); Shapiro S; Gershtein R; Kinarty A; Rawashdeh H; Honigman S; Lahat N. LADY DAVIS CARMEL MED CTR, NEUROIMMUNOL RES UNIT, 7 MICHAL ST, IL-34362 HAIFA, ISRAEL (Reprint); LADY DAVIS CARMEL MED CTR, MULTIPLE SCLEROSIS CTR, IL-34362 HAIFA, ISRAEL; LADY DAVIS CARMEL MED CTR, DEPT NEUROL, IL-34362 HAIFA, ISRAEL; TECHNION ISRAEL INST TECHNOL, FAC MED, HAIFA, ISRAEL; TECHNION ISRAEL INST TECHNOL, RAPPAPORT INST RES MED SCI, HAIFA, ISRAEL; LADY DAVIS CARMEL MED CTR, MOL IMMUNOL RES UNIT, IL-34362 HAIFA, ISRAEL. JOURNAL OF NEUROIMMUNOLOGY (1 DEC 1998) Vol. 92, No. 1-2, pp. 113-121. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0165-5728. Pub. country: ISRAEL. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The synthetic polypeptide copolymer-1 (Cop-1; Copaxone(R);

Glatiramer Acetate) has been recently approved as an effective **treatment** in relapsing multiple sclerosis (MS). A large body of evidence demonstrates that Cop-1 induces active suppression of CNS-**inflammatory** disease in animal models. However, Cop-1-mediated suppressor mechanisms have not yet been elucidated in humans. A 12-month open study following clinical and immunological parameters of ten relapsing MS patients treated with Cop-1 is presented. Relapse rates and disability scores (EDSS) were evaluated prior to and after 12 months of **treatment**. The immunological parameters assessed prior to and at 3 months' interval during **treatment** included serum levels of soluble IL-2 receptor (sIL-2R) and IL-IO as well as leukocyte cytokine mRNA expression of TNF alpha, IL-4 and TCF-beta. Copaxone **treatment** was found to lead to a significant reduction in the mean annual relapse rate (from 1.4 prior to **treatment** to 0.6 during **treatment**) and stabilization of disability in 90% of the patients. The **treatment** was accompanied by an elevation of serum IL-10 levels, suppression of the pro-**inflammatory** cytokine TNF alpha mRNA, and an elevation of the anti-**inflammatory** cytokines TGF-beta and IL-4 mRNAs in PBLs. These results suggest that the beneficial clinical effects of Copaxone in MS patients may be attributed to changes in activation of T cell subsets and a shift from Th1 to Th2/Th3 cytokine profile, probably leading to Cop-1-driven mechanisms of bystander suppression.

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L13           0 L7 AND OSTEOARTHRITIS

=> s l7 and multiple sclerosis
L14         126 L7 AND MULTIPLE SCLEROSIS

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L15           62 DUP REMOVE L14 (64 DUPLICATES REMOVED)

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L15  ANSWER 1 OF 62  EMBASE  COPYRIGHT 2003 ELSEVIER SCI. B.V.
2002303237  EMBASE  Cutting edge: Oral type I IFN-.tau. promotes a Th2 bias and
     enhances suppression of autoimmune encephalomyelitis by oral
     glatiramer acetate. Soos J.M.; Stuve O.; Youssef S.;
     Bravo M.; Johnson H.M.; Weiner H.L.; Zamvil S.S.. Dr. S.S. Zamvil,
     Department of Neurology, University of California, 521 Parnassus Avenue,
     San Francisco, CA 94143, United States. zamvil@itsa.ucsf.edu. Journal of
     Immunology  169/5 (2231-2235)  1 Sep 2002.
     Refs: 23.
     ISSN: 0022-1767. CODEN: JOIMA3. Pub. Country: United States. Language:
     English. Summary Language: English.
AB   IFN-.tau., a novel type I IFN that possesses immunomodulatory properties,
     lacks toxicity normally associated with other type I IFNs. We examined the
     effects of oral IFN-.tau. alone and in combination with oral
     glatiramer acetate in experimental allergic
     encephalomyelitis (EAE). By comparison of oral administration of
     IFN-.alpha., -.beta., and -.tau. to myelin basic protein-specific
     TCR-transgenic mice, we demonstrate these type I IFNs promote secretion of
     the Th2 cytokine IL-10 with similar efficiency. Whereas IFN-.alpha. and
     -.beta. induced IFN-.gamma. secretion, a Th1 cytokine, IFN-.tau. did not.
     Oral IFN-.tau. alone suppressed EAE. When suboptimal doses were
     administered orally in combination to wild-type mice, IFN-.tau. and
     glatiramer acetate had a synergistic beneficial effect
     in suppression of EAE. This combination was associated with TGF-.beta.
     secretion and enhanced IL-10 production. Thus, IFN-.tau. is a potential
     candidate for use as a single agent or in combination therapy for
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multiple sclerosis.

L15 ANSWER 2 OF 62 MEDLINE DUPLICATE 1
2003071203 Document Number: 22469139. PubMed ID: 12581542. A comparison of the mechanisms of action of interferon beta and **glatiramer acetate** in the **treatment** of **multiple sclerosis**. Zhang Jingwu; Hutton George; Zang Ying. (Department of Neurology, Baylor College of Medicine, Houston, Texas 77030, USA.. jzang@bcm.tmc.edu) . CLINICAL THERAPEUTICS, (2002 Dec) 24 (12) 1998-2021. Journal code: 7706726. ISSN: 0149-2918. Pub. country: United States. Language: English.

AB BACKGROUND: The development of immunomodulatory agents has represented a major advance in the **treatment** of **multiple sclerosis** (MS). To date, immunomodulatory agents approved for the **treatment** of relapsing MS in the United States include 3 forms of recombinant interferon (IFN) beta (2 formulations of IFN beta-1a and 1 of IFN beta-1b) and synthetic **glatiramer acetate** (GA). Recognition of how these agents work to regulate the immune system may lead to a better understanding of disease mechanisms, as well as to development of more effective therapies or combinations of therapy. OBJECTIVE: This article reviews the potential mechanisms of action of IFN beta products and GA in the context of their regulatory effects on **autoimmune** components that may be of importance in MS. METHODS: MEDLINE and Current Contents/Clinical Medicine were searched for articles published in English from 1993 to the present using the search terms interferon beta, **glatiramer acetate**, and **multiple sclerosis**. RESULTS: IFN beta products affect the disease process in MS through multiple potential mechanisms of action, including antiviral, antiproliferative, and anti-inflammatory effects. The mechanisms of action of GA are less clear, but may involve immune regulation induced by a gradual shift of T-cell phenotype from proinflammatory (type 1 T-helper cells) to anti-inflammatory (type 2 T-helper cells) and interference with antigen presentation. CONCLUSION: Understanding the mechanisms of action of IFN beta products and GA provides important insights into the disease processes involved in MS.

L15 ANSWER 3 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)
2002:532667 The Genuine Article (R) Number: 564MR. Novel synthetic amino acid copolymers that inhibit autoantigen-specific T cell responses and suppress experimental **autoimmune** encephalomyelitis. Fridkis-Hareli M; Santambrogio L; Stern J N H; Fugger L; Brosnan C; Strominger J L (Reprint) . Harvard Univ, Dept Mol & Cell Biol, 7 Divin Ave, Cambridge, MA 02138 USA (Reprint); Harvard Univ, Dept Mol & Cell Biol, Cambridge, MA 02138 USA; Dana Farber Canc Inst, Dept Canc Immunol & AIDS, Boston, MA 02115 USA; Aarhus Univ Hosp, Skejby Sygehus, Dept Clin Immunol, Aarhus N, Denmark; Albert Einstein Coll Med, Dept Pathol, Bronx, NY 10467 USA. JOURNAL OF CLINICAL INVESTIGATION (JUN 2002) Vol. 109, No. 12, pp. 1635-1643. Publisher: AMER SOC CLINICAL INVESTIGATION INC. 35 RESEARCH DR, STE 300, ANN ARBOR, MI 48103 USA. ISSN: 0021-9738. Pub. country: USA; Denmark. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Copolymer 1 (Cop 1, Copaxone [Teva Marion Partners, Kansas City, Missouri, USA]), a random amino acid copolymer of tyrosine (Y), glutamic acid (E), alanine (A), and lysine (K), reduces the frequency of relapses by 30% in relapsing-remitting **multiple sclerosis** (MS) patients. In the present study, novel random four-amino acid copolymers, whose design was based on the nature of the anchor residues of the immunodominant epitope of myelin basic protein (MBP) 85-99 and of the binding pockets of MS-associated HLA-DR2 (DRB1*1501), have been synthesized by solid-phase chemistry. Poly (Y, F, A, K) (YFAK) inhibited binding of the biotinylated MBP 86-100 epitope to HLA-DR2 molecules more efficiently than did either unlabeled MBP 85-99 or any other copolymer including Cop 1. Moreover, YFAK and poly (F, A, K) (FAK) were much more

effective than Cop 1 in inhibition of MBP 85-99-specific HLA-DR2-restricted T cell clones. Most importantly, these novel copolymers suppressed experimental **autoimmune** encephalomyelitis, induced in the susceptible SJL/J(H-2s) strain of mice with the encephalitogenic epitope PLP 139-151, more efficiently than did Cop 1. Thus, random synthetic copolymers designed according to the binding motif of the human immunodominant epitope MBP 85-99 and the binding pockets of HLA-DR2 might be more beneficial than Cop 1 in **treatment** of MS.

L15 ANSWER 4 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)
2002:799312 The Genuine Article (R) Number: 596JH. Differential mechanisms of action of interferon-beta and **glatiramer acetate** in MS
. Yong V W (Reprint). Univ Calgary, Dept Oncol, 3330 Hosp Dr, Calgary, AB T2N 4N1, Canada (Reprint); Univ Calgary, Dept Oncol, Calgary, AB T2N 4N1, Canada; Univ Calgary, Dept Clin Neurosci, Calgary, AB T2N 4N1, Canada. NEUROLOGY (24 SEP 2002) Vol. 59, No. 6, pp. 802-808. Publisher: LIPPINCOTT WILLIAMS & WILKINS. 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA. ISSN: 0028-3878. Pub. country: Canada. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Interferon-beta and **glatiramer acetate** (GA) are the two main groups of drugs used in the **treatment** of MS. Notably, while both ultimately decrease CNS inflammation, they do so by very different mechanisms. Interferon-beta has potent activity at the blood-brain barrier and impairs the trafficking of inflammatory cells into the CNS. In contrast, GA has negligible effect at the blood-brain barrier, allowing GA-specific T helper 2 lymphocytes to enter the CNS to decrease inflammation through bystander suppression. Other differences are also emphasized. The presence of GA-reactive lymphocytes within the CNS parenchyma may have the additional benefit of conferring neuroprotection through protective autoimmunity.

L15 ANSWER 5 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)
2002:240114 The Genuine Article (R) Number: 528AW. **Glatiramer acetate** (Copaxone) therapy induces CD8(+) T cell responses in patients with **multiple sclerosis**. Karandikar N J (Reprint); Crawford M P; Yan X; Ratts R B; Brenchley J M; Ambrozak D R; Lovett-Racke A E; Frohman E M; Stastny P; Douek D C; Koup D A; Racke M K. Univ Texas, SW Med Ctr, Dept Pathol, 5323 Harry Hines Blvd, Dallas, TX 75390 USA (Reprint); Univ Texas, SW Med Ctr, Dept Pathol, Dallas, TX 75390 USA; Univ Texas, SW Med Ctr, Dept Neurol, Dallas, TX 75390 USA; Univ Texas, SW Med Ctr, Dept Internal Med, Dallas, TX 75390 USA; Univ Texas, SW Med Ctr, Ctr Immunol, Dallas, TX 75390 USA. JOURNAL OF CLINICAL INVESTIGATION (MAR 2002) Vol. 109, No. 5, pp. 641-649. Publisher: AMER SOC CLINICAL INVESTIGATION INC. 35 RESEARCH DR, STE 300, ANN ARBOR, MI 48103 USA. ISSN: 0021-9738. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB **Glatiramer acetate** (GA; Copaxone) is a random copolymer of glutamic acid, lysine, alanine, and tyrosine that is used therapeutically in patients with **multiple sclerosis** (MS). To investigate the mechanism of the drug's immunomodulatory effect, we used immunophenotypic approaches to characterize the precise nature of GA-induced T cell responses. We demonstrate here that healthy individuals and untreated MS patients exhibit prominent T cell proliferative responses to GA. However, these responses are different in distinct subsets of T cells. Whereas GA-induced CD4(+) T cell responses are comparable in healthy individuals and MS patients, CD8(+) T cell responses are significantly lower in untreated MS patients. **Treatment** with GA results in upregulation of these CD8(+) responses with restoration to levels observed in healthy individuals. Both CD4(+) and CD8(+) GA-specific responses are HLA-restricted. GA therapy also induces a change in the cytokine profile of GA-specific CD4(+) and CD8(+) T cells. This study provides the first direct immunophenotypic evidence, to our knowledge, of GA-specific CD8(+) T cell responses and their upregulation during the

course of therapy, which may suggest a role for these responses in the immunomodulatory effects of the drug.

L15 ANSWER 6 OF 62 CAPLUS COPYRIGHT 2003 ACS
2002:203954 Document No. 137:72378 Degeneracy, as opposed to specificity, in immunotherapy. Hafler, David A. (Center for Neurologic Disease, Brigham and Women's Hospital and Harvard Medical School, Harvard Institutes of Medicine, Boston, MA, 02115, USA). Journal of Clinical Investigation, 109(5), 581-584 (English) 2002. CODEN: JCINAO. ISSN: 0021-9738. Publisher: American Society for Clinical Investigation.
AB A review discusses T-cell degeneracy as a **treatment** for human **autoimmune** disease using **glatiramer acetate** (GA). Karandikar et al. (2002) confirm that GA **treatment** causes a shift by CD4+ TY cells toward a Th2 or Th3 phenotype, based on the increased levels of TGF-.beta. mRNA and cell-assocd. interleukin-4. They have found that major histocompatibility class I-restricted CD8+ T cells in untreated **multiple sclerosis** patients respond weakly to GA. **Treatment** with GA stimulates these responses, restoring them to levels obsd. in healthy individuals. These cells may regain the ability to suppress myelin-reactive Th1 cells. GA may have more than one mechanism of action, inducing different effects in CD4+ and CD8+ T cells that work in sep. but parallel immune pathways.

L15 ANSWER 7 OF 62 MEDLINE DUPLICATE 2
2002651679 Document Number: 22298558. PubMed ID: 12412939. Prevention of **autoimmune** attack and disease progression in **multiple sclerosis**: current therapies and future prospects. Pender M P; Wolfe N P. Intern Med J, (2002 Nov) 32 (11) 554-63. Ref: 60. Journal code: 101092952. ISSN: 1444-0903. Pub. country: Australia. Language: English.
AB **Multiple sclerosis** (MS) is an important cause of progressive neurological disability, typically commencing in early adulthood. There is a need for safe and effective therapy to prevent the progressive central nervous system (CNS) damage and resultant disability that characterize the disease course. Increasing evidence supports a chronic **autoimmune** basis for CNS damage in MS. In the present study, we review current concepts of **autoimmune** pathogenesis in MS, assess current therapies aimed at countering **autoimmune** attack and discuss potential therapeutic strategies. Among currently available therapies, beta-interferon and **glatiramer acetate** have a modest effect on reducing relapses and slowing the accumulation of disability in relapsing-remitting MS. Beta-interferon is of doubtful efficacy in secondary progressive MS and appears to aggravate primary progressive MS, possibly by increasing antibody-mediated CNS damage through inhibition of B-cell apoptosis. Mitoxantrone may reduce relapses and slow disability progression in relapsing-remitting and secondary progressive MS, but its use is limited by the risk of cardiomyopathy. There are currently no effective **treatments** for primary progressive MS. Many therapies that are effective in the animal model, experimental **autoimmune** encephalomyelitis (EAE), are either ineffective in MS or--in the case of gamma-interferon, lenercept and altered peptide ligands--actually make MS worse. This discrepancy may be explained by the occurrence in MS of defects in immunoregulatory mechanisms, the integrity of which is essential for the efficacy of these **treatments** in EAE. It is likely that the development of safe, effective therapy for MS will depend on a better understanding of immunoregulatory defects in MS.

L15 ANSWER 8 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)
2002:989458 The Genuine Article (R) Number: 620HE. Effect of combined IFN beta-Ia and **glatiramer acetate** therapy on GA-specific T-cell responses in **multiple sclerosis**. Dhib-Jalbut S (Reprint); Chen M; Henschel K; Ford D; Costello K; Panitch H. Univ

Maryland Hosp, Dept Neurol, Rm N4W46, 22 S Greene St, Baltimore, MD 21201 USA (Reprint); Univ Maryland, Dept Neurol, Baltimore, MD 20742 USA; Baltimore VA Med Ctr, Baltimore, MD USA. MULTIPLE SCLEROSIS (DEC 2002) Vol. 8, No. 6, pp. 485-491. Publisher: ARNOLD, HODDER HEADLINE PLC. 338 EUSTON ROAD, LONDON NW1 3BH, ENGLAND. ISSN: 1352-4585. Pub. country: USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The combined **treatment** with interferon beta (IFNbeta) and **glatiramer acetate** (GA) is of current interest in **multiple sclerosis** (MS). The therapeutic effect of GA in MS is believed to be mediated by GA-specific Th2 cells. IFNbeta has a significant anti-proliferative effect on GA-induced lymphoproliferation in vitro. Therefore, we examined the possibility that IFNbeta may interfere with the generation and phenotype of GA T-cell responses in MS patients receiving combined therapy. Sixty-six GA-specific T-cell lines (TCL) were generated ex vivo from five MS patients enrolled in an open-label clinical trial of combined IFNbeta1GA **treatment** Controls included 83 pretreatment and 131 on-**treatment** GA-TCL from I I MS patients treated with GA only, and five GA-TCL generated from four patients receiving IFNbeta-1a monotherapy. IFN-gamma and IL-5 (markers of Th1 and Th2 responses, respectively) were assayed by ELISA in GA-TCL supernatants. Th1/Th2 bias was defined by the IFN-gamma/IL-5 level ratio (> 2 = Th I bias, < 0.5 = Th2 bias, and 0.5-2 = ThO bias). The frequency with which GA-reactive TCL were generated was 37.0% for the patients in the combination trial compared to 33.3% in the patients receiving GA alone. The mean stimulation index of the GA-TCL was 8.41 (range 2-42) for the combination compared to a mean of 6.29 (range 2-37) for the GA-treated group - a nonsignificant difference. Mean GA-TCL IFN-gamma production was significantly lower in all **treatment** groups compared to pretreatment. IL-5 levels were enhanced in all **treatment** groups compared to pretreatment levels, but the change was not statistically significant. The Th1/Th0/Th2 distribution of GA-TCL was 7%130%163% for the GA+IFNbeta group, 8%19%183% for the GA group, compared to 48%12%131% pre-GA **treatment**. All five GA-TCL from the IFNbeta-1a monotherapy patients were Th2-biased. We conclude that IFNbeta-1a does not affect the generation of GA-reactive T cells in vivo. Although more ThO GA-TCL occurred with combination therapy than with GA **treatment** alone, both groups shared an overall Th2 bias. Therefore, we speculate that combined therapy is unlikely to reduce the efficacy of GA **treatment** in MS.

L15 ANSWER 9 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)

2002:825012 The Genuine Article (R) Number: 600GG. **Treatment** of **multiple sclerosis** with the pregnancy hormone estriol. Sicotte N L; Liva S M; Klutch R; Pfeiffer P; Bouvier S; Odesa S; Wu T C J; Voskuhl R R (Reprint). Univ Calif Los Angeles, Reed Neurol Res Ctr, Dept Neurol, 710 Westwood Plaza, Los Angeles, CA 90095 USA (Reprint); Univ Calif Los Angeles, Reed Neurol Res Ctr, Dept Neurol, Los Angeles, CA 90095 USA; Univ Calif Los Angeles, Hlth Sci Ctr, Dept Obstet & Gynecol, Los Angeles, CA 90095 USA. ANNALS OF NEUROLOGY (OCT 2002) Vol. 52, No. 4, pp. 421-428. Publisher: WILEY-LISS. DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012 USA. ISSN: 0364-5134. Pub. country: USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Multiple sclerosis** patients who become pregnant experience a significant decrease in relapses that may be mediated by a shift in immune responses from T helper I to T,helper 2. Animal models of **multiple sclerosis** have shown that the pregnancy hormone, estriol, can ameliorate disease and can cause an immune shift. We treated nonpregnant female **multiple sclerosis** patients with the pregnancy hormone estriol in an attempt to recapitulate the beneficial effect of pregnancy. As compared with pretreatment baseline, relapsing remitting patients treated with oral estriol (8mg/day)

demonstrated significant decreases in delayed type hypersensitivity responses to tetanus, interferon-gamma levels in peripheral blood mononuclear cells, and gadolinium enhancing lesion numbers and volumes on monthly cerebral magnetic resonance images. When estriol **treatment** was stopped, enhancing lesions increased to pretreatment levels. When estriol. **treatment** was reinstituted, enhancing lesions again were significantly decreased. Based on these results, a larger, placebo-controlled trial of estriol is warranted in women with relapsing remitting **multiple sclerosis**. This novel **treatment** strategy of using pregnancy doses of estriol in **multiple sclerosis** has relevance to other **autoimmune** diseases that also improve during pregnancy.

L15 ANSWER 10 OF 62 MEDLINE
2002281059 Document Number: 22016759. PubMed ID: 12022056. [Historical aspects of **multiple sclerosis**]. Aspectos historicos de la esclerosis multiple. Moreira M A; Tilbery C P; Lana-Peixoto M A; Mendes M F; Kaimen-Maciel D R; Callegaro D. (Disciplina de Neurologia, Santa Casa, Sao Paulo SP, Brasil.. drmarcosmoreira@uol.com.br) . REVISTA DE NEUROLOGIA, (2002 Feb 16-28) 34 (4) 379-83. Journal code: 7706841. ISSN: 0210-0010. Pub. country: Spain. Language: Spanish.

AB INTRODUCTION: **Multiple sclerosis** (MS) is one of the most common diseases of the central nervous system (CNS) in young adults. MS is the most common disorder of the central nervous system in young people living in temperate climate regions. Although a few references to possible cases of the disease come from the xiii century, its scientific observation and systematic study only started in the late xix century. DEVELOPMENT: Robert Carswell e Jean Cruveilhier were the first investigators to document the pathological lesions while the clinical picture was first studied by Charcot. In spite of a huge number of infectious agents has been proposed for the etiology of MS and a genetic susceptibility trait recently defined, the ultimate cause of the disease remains to be determined. The development of diagnostic criteria sets, clinical disability scales and image methods in the latter half of the last century has provided investigators with useful research tools allowing unprecedented advances. In the last 30 years ACTH and corticosteroids have been employed as **treatment** for MS relapses. Starting in 1993 a new class of drugs called disease modifying agents, such as interferon beta and more recently **glatiramer acetate**, was introduced with encouraging results. CONCLUSIONS: MS is postulated to be a cell mediated **autoimmune** disease directed against CNS myelin components and characterized by inflammation and chronic demyelination. This paper is a review of the principal most significant events in the search for knowledge of the disease in the world.

L15 ANSWER 11 OF 62 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 3
2002222338 EMBASE [Historical aspects of **multiple sclerosis**]. ASPECTOS HISTORICOS DE LA ESCLEROSIS MULTIPLE. Moreira M.A.; Tilbery C.P.; Lana-Peixoto M.A.; Mendes M.; Kaimen-Maciel D.R.; Callegaro D.. Dr. M.A. Moreira, Rua Jaguaribe, 629-6B, CEP: 01224-001 Sao Paulo, Brazil. drmarcosmoreira@uol.com.br. Revista de Neurologia 34/4 (378-383) 16 Feb 2002.
Refs: 60.
ISSN: 0210-0010. CODEN: RVNRAA. Pub. Country: Spain. Language: Spanish. Summary Language: English; Spanish; Portuguese.

AB Introduction. **Multiple sclerosis** (MS) is one of the most common diseases of the central nervous system (CNS) in young adults. MS is the most common disorder of the central nervous system in young people living in temperate climate regions. Although a few references to possible cases of the disease come from the XIII century, its scientific observation and systematic study only started in the late XIX century. Development. Robert Carswell e Jean Cruveilhier were the first

investigators to document the pathological lesions while the clinical picture was first studied by Charcot. In spite of a huge number of infectious agents has been proposed for the etiology of MS and a genetic susceptibility trait recently defined, the ultimate cause of the disease remains to be determined. The development of diagnostic criteria sets, clinical disability scales and image methods in the latter half of the last century has provided investigators with useful research tools allowing unprecedented advances. In the last 30 years ACTH and corticosteroids have been employed as **treatment** for MS relapses. Starting in 1993 a new class of drugs called disease modifying agents, such as interferon beta and more recently **glatiramer acetate**, was introduced with encouraging results. Conclusions. MS is postulated to be a cell-mediated **autoimmune** disease directed against CNS myelin components and characterized by inflammation and chronic demyelination. This paper is a review of the principal most significant events in the search for knowledge of the disease in the world.

L15 ANSWER 12 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)
2002:505133 The Genuine Article (R) Number: 560GT. Anti-inflammatory strategies to prevent axonal injury in **multiple sclerosis**. Rieckmann P (Reprint); Maurer M. Univ Wurzburg, Dept Neurol, Clin Res Unit Multiple Sclerosis & Neuroimmunol, Josef Schneider Str 11, D-97080 Wurzburg, Germany (Reprint); Univ Wurzburg, Dept Neurol, Clin Res Unit Multiple Sclerosis & Neuroimmunol, D-97080 Wurzburg, Germany . CURRENT OPINION IN NEUROLOGY (JUN 2002) Vol. 15, No. 3, pp. 361-370. Publisher: LIPPINCOTT WILLIAMS & WILKINS. 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA. ISSN: 1350-7540. Pub. country: Germany. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Axonal injury in **multiple sclerosis** has attracted considerable interest during the past few years. It has been demonstrated in association with inflammation within active lesions, but it is also present in normal-appearing white matter. Because axonal loss appears to be responsible for persistent neurological deficits in patients with **multiple sclerosis, treatment** strategies to prevent damage to neurites and restore function are of paramount importance in controlling the disease process. Some of the currently available immunomodulatory therapies may also reduce axonal damage, as demonstrated using improved imaging technologies, but the precise mechanisms that could protect axons during the inflammatory attack are yet to be identified. Factors that are involved in functional impairment of axonal conduction and those elements that are responsible for direct structural damage to the axon are both potential targets for therapeutic interventions.

L15 ANSWER 13 OF 62 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 4
2002338506 EMBASE [Immunotherapy of **multiple sclerosis** with **glatiramer acetate** mechanisms of action and results from therapeutic trials]. IMMUNTHERAPIE DER MULTIPLEN SKLEROSE MIT GLATIRAMERAZETAT (COPAXONE.RTM.): WIRKMECHANISMEN UND ERGEBNISSE AUS THERAPIESTUDIEN. Gold R.; Heidenreich F.; Kappos L.. Dr. R. Gold, Neurologische Universitatsklinik, Josef-Schneider-Strasse 11, 97080 Wurzburg, Germany. r.gold@mail.uni-wuerzburg.de. Aktuelle Neurologie 29/7 (345-351) 2002.
Refs: 31.
ISSN: 0302-4350. CODEN: AKNUAR. Pub. Country: Germany. Language: German. Summary Language: English; German.

AB Amongst immunomodulatory drugs used in **multiple sclerosis** (MS), **glatiramer acetate** (GLAT: former name: Copolymer-1: trademark Copaxone) has the longest history. Even today its mechanisms of action are only incompletely understood. GLAT has shown therapeutic efficacy in diverse models of experimental **autoimmune** encephalomyelitis (EAE). At the cellular level GLAT

induces a shift from TH1 to TH2 cytokines. Therapeutic efficacy in relapsing-remitting MS patients has been proven by controlled clinical studies. Here we review current aspects of GLAT therapy and discuss its role in immunomodulatory **treatment** of MS.

L15 ANSWER 14 OF 62 MEDLINE DUPLICATE 5
2002300315 Document Number: 22037310. PubMed ID: 12040979. [**Treatment** of **multiple sclerosis** with **glatiramer acetate**. Current aspects of mechanisms of action, pharmacokinetics, adverse effect profile and clinical studies]. Behandlung der Multiplen Sklerose mit Glatiramer-Azetat. Aktuelles zu Wirkungsmechanismen, Pharmakokinetik, Nebenwirkungsprofil und Studiensituation. Ziemssen T; Neuhaus O; Farina C; Hartung H P; Hohlfeld R. (Abteilung fur Neuroimmunologie, Max-Planck-Institut fur Neurobiologie, Martinsried.) NERVENARZT, (2002 Apr) 73 (4) 321-31. Ref: 82. Journal code: 0400773. ISSN: 0028-2804. Pub. country: Germany: Germany, Federal Republic of. Language: German.

AB **Glatiramer acetate** (GA, Copaxone), a standardized mixture of synthetic polypeptides, has now been approved also in Germany for the **treatment** of relapsing-remitting **multiple sclerosis** (RR-MS). After it had been shown effective in suppression of experimental **autoimmune** encephalomyelitis (EAE), the animal model of **multiple sclerosis** (MS), it was evaluated in several clinical studies. In these studies, GA could alter the natural history of MS by both reducing the relapse rate and affecting disability. The clinical therapeutic effect of GA was consistent with the effect on magnetic resonance imaging-defined disease activity and burden in a recent multicenter study. As a daily standard dose, 20 mg of GA is injected subcutaneously. The induction of GA-reactive T-helper 2-like regulatory suppressor cells is thought to be the main mechanism of action. The most common adverse effects are mild injection site reactions. A remarkable but rare adverse effect is the only transient immediate post-injection systemic reaction manifested by flushing, chest tightness, palpitations, and dyspnea. Antibodies to GA which are induced during GA **treatment** do not interfere with its clinical effects.

L15 ANSWER 15 OF 62 MEDLINE DUPLICATE 6
2002370515 Document Number: 22111371. PubMed ID: 12114110. Dual action of **glatiramer acetate** (Cop-1) in the **treatment** of CNS **autoimmune** and neurodegenerative disorders. Kipnis Jonathan; Schwartz Michal. (Dept of Neurobiology, The Weizmann Institute of Science, 76100 Rehovot, Israel.) Trends Mol Med, (2002 Jul) 8 (7) 319-23. Ref: 64. Journal code: 100966035. ISSN: 1471-4914. Pub. country: England: United Kingdom. Language: English.

AB Protective autoimmunity is the body's defense mechanism against destructive self-compounds such as those commonly associated with neurodegenerative disorders. **Autoimmune** disease and neurodegenerative disorders can thus be viewed as two extreme manifestations of the same process. Therefore, when designing therapy, it is important to avoid an approach that will cure the one by invoking the other. One way to stop, or at least slow down, the progression of neurodegeneration without risking development of an **autoimmune** disease is by boosting protective autoimmunity in a well-controlled way. Copolymer 1 (Cop-1), an approved drug for the **treatment** of **multiple sclerosis**, can be used as a **treatment** for **autoimmune** diseases and as a therapeutic vaccine for neurodegenerative diseases. We propose that the protective effect of Cop-1 vaccination is obtained through a well-controlled inflammatory reaction, and that the activity of Cop-1 in driving this reaction derives from its ability to serve as a 'universal antigen' by weakly activating a wide spectrum of self-reactive T cells.

L15 ANSWER 16 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)

2002:600857 The Genuine Article (R) Number: 572XM. Cytokine production in T lymphocyte-microglia interaction is attenuated by **glatiramer acetate**: a mechanism for therapeutic efficacy in **multiple sclerosis**. Chabot S; Yong F P; Le D M; Metz L M; Myles T; Yong V W (Reprint). Univ Calgary, Neurosci Res Grp, Fac Med, Dept Clin Neurosci, 3330 Hosp Dr NW, Calgary, AB T2N 4N1, Canada (Reprint); Univ Calgary, Neurosci Res Grp, Fac Med, Dept Clin Neurosci, Calgary, AB T2N 4N1, Canada; Univ Calgary, Fac Med, Dept Oncol, Calgary, AB T2N 4N1, Canada. MULTIPLE SCLEROSIS (AUG 2002) Vol. 8, No. 4, pp. 299-306. Publisher: ARNOLD, HODDER HEADLINE PLC. 338 EUSTON ROAD, LONDON NW1 3BH, ENGLAND. ISSN: 1352-4585. Pub. country: Canada. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The efficacy of **glatiramer acetate** in **multiple sclerosis** (MS) is thought to involve the production of Th2 regulatory lymphocytes that secrete anti-inflammatory cytokines, however, other mechanisms cannot be excluded. Given that activated T lymphocytes infiltrate into the CNS and become in close proximity to microglia, we evaluated whether **glatiramer acetate** affects the potential interaction between T cells and microglia. We report that the co-culture of activated T lymphocytes with microglia led to the induction of several cytokines, and that these were reduced by **glatiramer acetate treatment**. Morphological transformation of bipolar/ramified microglia into an activated ameboid form was attenuated by **glatiramer acetate**. These results reveal a novel mechanism for **glatiramer acetate**: the impairment of activated T cells to effectively interact with microglia to produce cytokines. The net result of a non-inflammatory milieu within the CNS, in spite of T cell infiltration, may help account for the amelioration of disease activity in MS patients on **glatiramer acetate** therapy.

L15 ANSWER 17 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)
2002:840657 The Genuine Article (R) Number: 600ZV. Approved and future pharmacotherapy for **multiple sclerosis**. Stuve O (Reprint); Cree B C; von Budingen H C; Yousef S; Bowen J D; Genain C P; Hauser S L; Steinman L; Zamvil S S. Univ Calif San Francisco, Dept Neurol, San Francisco, CA 94143 USA; Univ Washington, Dept Neurol, Seattle, WA 98195 USA; Stanford Univ, Dept Neurol, Stanford, CA 94305 USA. NEUROLOGIST (SEP 2002) Vol. 8, No. 5, pp. 290-301. Publisher: LIPPINCOTT WILLIAMS & WILKINS. 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA. ISSN: 1074-7931. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB BACKGROUND- Pharmacotherapy for relapsing-remitting **multiple sclerosis** (MS) advanced with the demonstration that interferon beta and **glatiramer acetate** improve the clinical course of this disease. Mitoxantrone is the first drug approved by the Food and Drug Administration for **treatment** of secondary progressive MS. Despite this progress, the agents presently available are only partially effective, are difficult to administer, and may have significant side effects. Several orally administered immunomodulatory agents are presently being evaluated for **treatment** of MS. One class of drugs, HMG CoA inhibitors (statins), is safe and well-tolerated and could become another mainstay of MS therapy.

REVIEW SUMMARY- This article reviews the clinical evidence for approved MS therapies and discusses their mechanisms of action. Furthermore, the clinical and laboratory data suggesting a potential role for statins in MS therapy are discussed.

CONCLUSIONS- Although **treatment** with interferon beta, **glatiramer acetate**, and mitoxantrone, the approved therapies, provide important **treatment** options for patients with relapsing-remitting MS and secondary progressive MS, the potential benefits of other medications, including statins, should be explored in controlled clinical trials.

L15 ANSWER 18 OF 62 MEDLINE DUPLICATE 7
2002147407 Document Number: 21676149. PubMed ID: 11818475.
Multiple sclerosis. Keegan B Mark; Noseworthy John H. (Department of Neurology, Mayo Clinic and Mayo Foundation, 200 First Street SW, Rochester, Minnesota 55905, USA.) ANNUAL REVIEW OF MEDICINE, (2002) 53 285-302. Ref: 95. Journal code: 2985151R. ISSN: 0066-4219. Pub. country: United States. Language: English.

AB **Multiple sclerosis** (MS) is a common inflammatory disease of the central nervous system (CNS). Diagnosis rests upon identifying typical clinical symptoms and interpreting supportive laboratory and radiological investigations. The etiology is unknown; however, strong evidence suggests that MS is an **autoimmune** disease directed against CNS myelin or oligodendrocytes. Genetic factors are important in the development of MS. Contributing environmental determinants (possibly including infectious agents) appear important but remain unidentified. Both cell-mediated and humorally mediated immune mechanisms contribute to pathological injury. Axonal damage occurs in addition to demyelination and may be the cause of later permanent disability. Distinct pathological subtypes may differentiate among patients with MS. **Treatment** is directed at acute attacks (with corticosteroids) and reduction of attack frequency (primarily with type-1 beta interferons and **glatiramer acetate**). Research into the causes and **treatments** of MS has expanded our knowledge of this disease and promises improved care for MS patients in the future.

L15 ANSWER 19 OF 62 MEDLINE DUPLICATE 8
2002292284 Document Number: 22028658. PubMed ID: 12031214.
Glatiramer acetate. Comi G; Moiola L. (Head of the Departments of Neurology and Neurophysiology, University Vita-Salute San Raffaele, Milan, Italy.) NEUROLOGIA, (2002 May) 17 (5) 244-58. Ref: 91. Journal code: 9005460. ISSN: 0213-4853. Pub. country: Spain. Language: English.

AB **Glatiramer acetate** (GA) is a mixture of synthetic polypeptides composed of four aminoacids. GA is very effective in suppression of experimental **autoimmune** encephalomyelitis (EAE), the animal model of **multiple sclerosis** (MS). Various mechanisms of action of GA have been proposed, but the most important is probably the induction of antigen-specific suppressor T cells. Class one clinical trials have demonstrated that GA reduces the relapse rate and the accumulation of disability in relapsing-remitting (RR) MS. The positive effects on disease activity and disease progression are explained by the reduction of the number and volume of the active lesions as showed by Magnetic resonance imaging (MRI) studies. Moreover new MRI techniques suggest that GA may also have some neuroprotective effects. The drug is usually well tolerated with modest side effects. In vitro and in vivo animal studies have shown that GA is devoid of teratogenic or mutagenic effects. GA is a good alternative to interferon beta for **treatment** of RR-MS.

L15 ANSWER 20 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)
2002:665235 The Genuine Article (R) Number: 581HH. Therapeutic approaches in **multiple sclerosis** - Lessons from failed and interrupted **treatment** trials. Wiendl H (Reprint); Hohlfeld R. Univ Tubingen, Sch Med, Dept Neurol, Hoppe Seyler Str 3, D-72076 Tubingen, Germany (Reprint); Univ Tubingen, Sch Med, Dept Neurol, D-72076 Tubingen, Germany; Klinikum Grosshadern, Inst Clin Neuroimmunol, Munich, Germany; Max Planck Inst Neurobiol, Dept Neuroimmunol, Martinsried, Germany. BIODRUGS (JUL 2002) Vol. 16, No. 3, pp. 183-200. Publisher: ADIS INTERNATIONAL LTD. 41 CENTORIAN DR, PRIVATE BAG 65901, MAIRANGI BAY, AUCKLAND 10, NEW ZEALAND. ISSN: 1173-8804. Pub. country: Germany. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The therapy for **multiple sclerosis** (MS) has changed

dramatically over the past decade. Recent immunobiological findings and current pathophysiological concepts together with advances in biotechnology, improvements in clinical trial design and development of magnetic resonance imaging have led to a variety of evaluable therapeutic approaches in MS. However, in contrast to the successfully introduced and established immunomodulatory therapies (e.g. interferon-beta and **glatiramer acetate**), there have been a remarkable number of therapeutic failures as well. Despite convincing immunological concepts, impressive data from animal models and promising results from phase I/II studies, the drugs and strategies investigated showed no benefit or even turned out to have unexpectedly severe adverse effects.

Although to date there is no uniformly accepted model for MS, there is agreement on the significance of inflammatory events mediated by autoreactive T cells in the CNS. These can be modified therapeutically at the individual steps of a hypothetical pathogenetic cascade. Crucial corners like: (i) the prevalence and peripheral activation of CNS-autoreactive T cells in the periphery; (ii) adhesion and penetration of T cells into the CNS; (iii) local activation and proliferation and; (iv) de- and remyelination processes can be targeted through their putative mediators. Like a 'specificity pyramid', therapeutic approaches therefore cover from general immunosuppression up to specific targeting of T-cell receptor peptide major histocompatibility (MHC) complex.

We discuss in detail clinical MS trials that failed or were discontinued for other reasons. These trials include cytokine modulators [tumour necrosis factor (TNF)-alpha antagonists, interleukin-10, interleukin-4, transforming growth factor-beta2], immunosuppressive agents (roquininex, gusperimus, sulfasalazine, cladribine), inducers of remyelination [intravenous immunoglobulins (IVIg)], antigen-derived therapies [oral tolerance, altered peptide ligands (APL), MHC-Peptide blockade], T cell and T-cell receptor directed therapies (T cell vaccination, T-cell receptor peptide vaccination), monoclonal antibodies against leucocyte differentiation molecules (anti-CD3, anti-CD4), and inactivation of circulating T cells (extracorporeal photopheresis).

The main conclusions that can be drawn from these 'negative' experiences Lire as follows. Theoretically promising agents may paradoxically increase disease activity (lenercept, inflixiniab), be associated with unforeseen adverse effects (e.g. roquinimex) or short-term favourable trends may reverse with prolonged follow-up (e.g. sulfasalzine). One should not be too enthusiastic about successful trials in animal models (TNFalpha blockers; oral tolerance; remyelinating effect of IVIg) nor be irritated by non-scientific media hype (deoxyspergualine; bone marrow transplantation). More selectivity can imply less efficacy (APL, superselective interventions like T-cell receptor vaccination) and antigen-related therapies can stimulate rather than inhibit encephalitogenic cells. Failed strategies are of high importance for a critical revision of assumed immunopathological mechanisms, their neuroimaging correlates, and for future trial design. Since failed trials add to our growing understanding of **multiple sclerosis**, 'misses' are nearly as important to the scientific process as the 'hits'.

L15 ANSWER 21 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)

2003:134264 The Genuine Article (R) Number: 639DC. Interleukin 12 and interleukin 10 are affected differentially by **treatment** of **multiple sclerosis** with **glatiramer acetate** (Copaxone). Losy J (Reprint); Michalowska-Wender G; Wender M. Univ Sch Med, Dept Clin Neuroimmunol, PL-60355 Poznan, Poland; Polish Acad Sci, Med Res Ctr, Neuroimmunol Unit, Poznan, Poland. FOLIA NEUROPATHOLOGICA (30 JAN 2002) Vol. 40, No. 4, pp. 173-175. Publisher: VIA MEDICA. UL SWIETOKRZYSKA 73, 80-180 GDANSK, POLAND. ISSN: 1641-4640. Pub. country: Poland. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Proinflammatory cytokines produced by Th-1 cells and cytokines with

immunosuppressive properties play an important role in the pathogenesis of **multiple sclerosis** (MS). **Glatiramer acetate** (GA) is one of the most important immunomodulatory agents used in the therapy of MS. The mechanism of action of GA in MS is not yet fully explained. In our previous study we found the significant down-regulation of interleukin 18 (IL-18), a proinflammatory cytokine inducing the production of interferon gamma during therapy with GA in MS patients. The purpose of this study was to evaluate the effect of GA in a dose 20 mg daily in a period of 6 months on interleukins IL-10 and IL-12. Thirty-one patients with definite MS and 30 control subjects were the subject of our study. The interleukins levels in sera were measured by the ELISA test. A significant increase was found of IL-12 and also of IL-10 levels in MS patients in comparison with control group. We also established a significant decrease of IL-12 after 3 and 6 months of GA therapy and some insignificant differences in the level of IL-10 (the decrease after 3 months and the increase after 6 months). IL-12 is a proinflammatory cytokine secreted by blood mononuclear cells, including dendritic cells in response to antigens and mitogens and is thought to contribute to the pathogenesis of MS. Therefore the established downregulation of IL-12 as well as that previously described of IL-18 suggest a marked relationship between the clinical effect and downregulatory action of GA on proinflammatory interleukins. The insignificant change of IL-10 level observed in the course of GA therapy seems to indicate that this cytokine is not connected with the immunomodulatory effect of GA in MS.

L15 ANSWER 22 OF 62 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 9

2002328715 EMBASE Prospects for therapeutic vaccination with **glatiramer acetate** for neurodegenerative diseases such as Alzheimer's disease. Schwartz M.; Kipnis J.. M. Schwartz, Department of Neurobiology, Weizmann Institute of Science, Rehovot 76100, Israel. michal.schwartz@weizmann.ac.il. Drug Development Research 56/2 (143-149) 2002.

Refs: 64.

ISSN: 0272-4391. CODEN: DDREDK. Pub. Country: United States. Language: English. Summary Language: English.

AB Neurodegenerative diseases, whatever their primary causes, are characterized by certain common features, one of which is their self-perpetuating nature. The ongoing progression of the disorder is due to the effects of destructive self-compounds, whose presence in the tissues is an outcome of the early phase of the disease and which gradually destroy remaining functional neurons. Studies in our laboratory have led to the recent formulation of a novel concept of protective autoimmunity as the body's mechanism of defense against these destructive self-compounds. This **autoimmune** response to central nervous system (CNS) insults is mediated by T-cells and presumably operates by activating and regulating local microglia and infiltrating macrophages (inflammatory response) to carry out their function of clearing destructive material from the tissue at risk. We suggest that a well-controlled autoimmunity counteracts and overcomes the destructive effects of the potentially harmful self-compounds, at the cost of some loss of tissue. An additional risk to the individual is the induction of an **autoimmune** disease, which is likely to occur if the **autoimmune** response is malfunctioning. An optimal balance of the various factors will lead to an outcome of maximal benefit at minimal cost to the tissue. A procedure for safely boosting the **autoimmune** response, by vaccination with a weak self-crossreactive antigen such as **glatiramer acetate** (also known as Cop-1) was found to protect rats from glutamate toxicity, a major mediator of the spread of damage and a well-known causative factor in neurodegenerative disorders. Cop-1, when administered according to a different regimen, is an FDA-approved drug for the **treatment** of **multiple sclerosis**. Different formulations of the same drug can therefore

be used to treat two extreme manifestations of chronic degenerative diseases of the CNS. .COPYRGT. 2002 Wiley-Liss, Inc.

L15 ANSWER 23 OF 62 MEDLINE DUPLICATE 10
2002251629 Document Number: 21986268. PubMed ID: 11990872.
Treatment of **multiple sclerosis** with cyclophosphamide: critical review of clinical and immunologic effects. Weiner H L; Cohen J A. (Multiple Sclerosis Center, Brigham and Women's Hospital, Massachusetts General Hospital, Harvard Medical School, Boston 02115, USA.. hweiner@rics.bwh.harvard.edu) . MULTIPLE SCLEROSIS, (2002 Apr) 8 (2) 142-54. Ref: 95. Journal code: 9509185. ISSN: 1352-4585. Pub. country: England: United Kingdom. Language: English.
AB Cyclophosphamide is an alkylating agent used to treat malignancies and immune-mediated inflammatory non-malignant processes such as lupus nephritis and immune-mediated neuropathies. It has been studied as a **treatment** for **multiple sclerosis** (MS) for the past 30 years and is used by physicians in selected cases of progressive or worsening MS. Review of published reports suggests that it is efficacious in cases of worsening MS that have an inflammatory component as evidenced by relapses and/or gadolinium (Gd)-enhancing lesions on magnetic resonance imaging (MRI) or in patients in earlier stages of disease where inflammation predominates over degenerative processes in the central nervous system (CNS). There is no evidence of efficacy in primary progressive MS or later stages of secondary progressive MS. Although a general immunosuppressant that affects both T- and B-cell function, cyclophosphamide has selective immune effects in MS by suppressing IL-12 and Th1-type responses and enhancing Th2/Th3 responses (IL-4, IL-10, TGF-beta; eosinophils in peripheral blood). Side effects include nausea, alopecia, infertility, bladder toxicity and risk of malignancy. The most commonly used regimens involve every 4- to 8-week outpatient i.v. pulse therapy given with or without corticosteroids and are usually well-tolerated by patients. Cyclophosphamide is currently used in patients whose disease is not controlled by beta-interferon or **glatiramer acetate** and those with rapidly worsening MS.

L15 ANSWER 24 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)
2002:746597 The Genuine Article (R) Number: 589PJ. Sustained immunological effects of **Glatiramer acetate** in patients with **multiple sclerosis** treated for over 6 years. Chen M; Conway K; Johnson K P; Martin R; Dhib-Jalbut S (Reprint). Univ Maryland Hosp, Dept Neurol, Rm N4W46, 22 S Greene St, Baltimore, MD 21201 USA (Reprint); Univ Maryland, Sch Med, Baltimore, MD 21201 USA; NINDS, Neuroimmunol Branch, NIH, Bethesda, MD 20892 USA; Baltimore VA Med Ctr, Baltimore, MD 21201 USA. JOURNAL OF THE NEUROLOGICAL SCIENCES (15 SEP 2002) Vol. 201, No. 1-2, pp. 71-77. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0022-510X. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The availability of a group of **multiple sclerosis** (MS) patients at the University of Maryland, who had participated in the pivotal Copaxones trial in the early 1990s, provided an opportunity to examine the long-term immunologic effects of **Glatiramer acetate** (GA) **treatment** in MS. Forty-eight GA-reactive T-cell lines (TCL) were generated from 10 MS patients who have been receiving GA **treatment** for 6-9 years. Proliferative responses, cytokine production, and cross-reactivity with myelin basic protein (MBP) and the MBP immunodominant peptide 83-99 were compared to responses obtained from 10 MS patients who were tested pretreatment and after a shorter period of **treatment** ranging from 1 to 10 months. The results indicate that while long-term **treatment** with GA results in a 2.9-fold decrease in the estimated precursor frequency of GA-reactive T-cells, the sustained response to GA remains Th2-biased and in part cross-reactive with MBP and MBP (83-99) as measured by proliferation and

cytokine release assays. The results indicate that despite a drop in the precursor frequency of GA-reactive T-cells with long-term **treatment**, the sustained response remains predominantly Th2-biased and cross-reactive with MBP, which is consistent with the anti-inflammatory effects of the drug and bystander suppression. (C) 2002 Elsevier Science B.V. All rights reserved.

L15 ANSWER 25 OF 62 MEDLINE DUPLICATE 11
2002280552 Document Number: 22015965. PubMed ID: 12020957. Oral **treatment** of mice with copolymer 1 (**glatiramer acetate**) results in the accumulation of specific Th2 cells in the central nervous system. Aharoni Rina; Meshorer Asher; Sela Michael; Arnon Ruth. (Department of Immunology, The Weizmann Institute of Science, PO Box 26, Rehovot 76100, Israel.) JOURNAL OF NEUROIMMUNOLOGY, (2002 May) 126 (1-2) 58-68. Journal code: 8109498. ISSN: 0165-5728. Pub. country: Netherlands. Language: English.
AB Mucosal administration of copolymer 1 (Cop 1, Copaxone(R), **glatiramer acetate**) suppresses experimental **autoimmune** encephalomyelitis (EAE), and is currently tested for its efficacy in the **treatment** of **multiple sclerosis** (MS). Here we demonstrate that oral **treatment** with Cop 1 induces, in mice, specific Th2 cells in the central nervous system (CNS), as manifested by their isolation from brains of actively sensitized Cop 1-fed mice, as well as, by the localization of orally induced Cop 1 specific suppressor cells in the brain, after their passive transfer to the periphery. Feeding with Cop 1 results in the accumulation in the CNS of cells that secrete Th2 cytokines in response to either Cop 1 or the autoantigen myelin basic protein (MBP), even in Th1 shifting environment, which consequently would lead to therapeutic effect in the MS diseased organ.

L15 ANSWER 26 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)
2002:364858 The Genuine Article (R) Number: 544VH. Considerations in the **treatment** of relapsing-remitting **multiple sclerosis**. Calabresi P A (Reprint). Univ Maryland, Med Syst, Dept Neurol, 22 S Greene St, Baltimore, MD 21201 USA (Reprint); Univ Maryland, Med Syst, Dept Neurol, Baltimore, MD 21201 USA. NEUROLOGY (23 APR 2002) Vol. 58, No. 8, Supp. [4], pp. S10-S22. Publisher: LIPPINCOTT WILLIAMS & WILKINS. 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA. ISSN: 0028-3878. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Disease-modifying drugs are available in the United States for the **treatment** of relapsing-remitting **multiple sclerosis** (RRMS), including interferon (IFN) beta-1a, IFNbeta-1b, and **glatiramer acetate**. Another formulation of IFNbeta-1a is available in Europe, Canada, and other countries. Mitoxantrone is also indicated for the **treatment** of worsening forms of RRMS and secondary progressive (SP) MS. In addition to reductions in annual relapse rates and other measures of clinical disability, the disease-modifying drugs appear to reduce MRI measures of disease activity. Available data suggest that the efficacy of disease-modifying therapy is sustained for at least for 4 to 6 years. Results of clinical drug trials have been used as a rationale to support **treatment** of early MS with a disease-modifying drug. Other medical therapies are used in the management of RRMS, including **treatments** to help manage MS-related symptoms such as spasticity and bladder dysfunction, and corticosteroids to hasten recovery from acute relapses. In some situations, interventions are used to minimize side effects of disease-modifying drug therapy. Several currently marketed **treatments**, including IV immunoglobulin, methotrexate, and azathioprine, are being evaluated as **treatments** for RRMS in combination with the approved therapies. Investigational compounds, including oral formulations of **glatiramer acetate** and

interferon, are in various stages of development.

L15 ANSWER 27 OF 62 CAPLUS COPYRIGHT 2003 ACS
2001:833075 Document No. 135:367223 Method of treating immune pathologies with low dose estrogen. Offner, Halina (Oregon Health Sciences University, USA; The Government of the United States of America). PCT Int. Appl. WO 2001085154 A2 20011115, 107 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US40710 20010511. PRIORITY: US 2000-PV203980 20000512.

AB The invention provides a method of ameliorating a Th1-mediated immune pathol. in a mammal. The method is practiced by administering a low dose of estrogen to the mammal. Optionally, an immunotherapeutic agent can also be administered to the mammal. Also provided are kits contg. a low dose of estrogen and an immunotherapeutic agent. The immunomodulatory agent is a cytokine or a peptide selected from the group consisting of an antigen peptide, an HLA peptide, a T cell receptor peptide or an analog of any of these peptides.

L15 ANSWER 28 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)
2001:485301 The Genuine Article (R) Number: 440CR. **Glatiramer acetate** inhibition of tumor necrosis factor-alpha-induced RANTES expression and release from U-251 MG human astrocytic cells. Li Q D Q (Reprint); Burt D R; Bever C T. 7806 Havenside Terrace, Rockville, MD 20855 USA (Reprint); Univ Maryland, Sch Med, Dept Neurol, Baltimore, MD USA; Univ Maryland, Sch Med, Dept Pharmacol & Expt Therapeut, Baltimore, MD USA; VA Maryland Hlth Care Syst, Med Res Serv, Baltimore, MD USA. JOURNAL OF NEUROCHEMISTRY (JUN 2001) Vol. 77, No. 5, pp. 1208-1217. Publisher: BLACKWELL SCIENCE LTD. P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND. ISSN: 0022-3042. Pub. country: USA. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB **Glatiramer acetate** is an approved drug for the **treatment** of **multiple sclerosis** (MS). RANTES is a beta -family chemokine that manifests chemoattractant activity for T lymphocytes and monocytes/macrophages implicated in the pathogenesis of MS lesions, However, the effect of **glatiramer acetate** on the regulation of RANTES secretion in glial cells is unknown. In the present study, we demonstrate for the first time that **treatment** of human U-251 MG astrocytic cells with **glatiramer acetate** blocks tumor necrosis factor-alpha (TNF-alpha)-induced RANTES mRNA and protein in a dose- and time-dependent manner. This effect is attributed to inhibition of transcription and a 40% decrease in transcript stability. Furthermore, our electrophoretic mobility shift assays of nuclear extracts from TNF-a-treated cells reveal an increase in DNA-binding activity specific for the nuclear factor-kappa B (NF-kappaB) binding site, in the 5 ' -flanking promoter region of the human RANTES gene, and that this increase in NF-kappaB binding activity is prevented by pretreatment with **glatiramer acetate** or the NF-kappaB inhibitors. These findings suggest that **glatiramer acetate** may exert its therapeutic effect in MS partially through inhibiting NF-kappaB activation and chemokine production.

L15 ANSWER 29 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)
2001:897964 The Genuine Article (R) Number: 490EA. Expression of urokinase plasminogen activator receptor on monocytes from patients with relapsing-remitting **multiple sclerosis**: Effect of **glatiramer acetate** (Copolymer 1). Balabanov R; Lisak D;

Beaumont T; Lisak R P; Dore-Duffy P (Reprint). Wayne State Univ, Sch Med, Detroit Med Ctr, Dept Neurol, Div Neuroimmunol, Multiple Sclerosis Clin Res Ctr, 421 E Canfield, 3124 Elliman, Detroit, MI 48201 USA (Reprint); Wayne State Univ, Sch Med, Detroit Med Ctr, Dept Neurol, Div Neuroimmunol, Multiple Sclerosis Clin Res Ctr, Detroit, MI 48201 USA; Univ Chicago Hosp, Dept Neurol, Chicago, IL 60637 USA. CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY (NOV 2001) Vol. 8, No. 6, pp. 1196-1203. Publisher: AMER SOC MICROBIOLOGY. 1752 N ST NW, WASHINGTON, DC 20036-2904 USA. ISSN: 1071-412X . Pub. country: USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Multiple sclerosis** (MS) is a chronic inflammatory disease of the central nervous system in which peripheral blood monocytes play an important role. We have previously reported that patients with chronic progressive MS (CPMS) have significantly increased numbers of circulating monocytes which express the urokinase plasminogen activator receptor (uPAR). In the present study, we examined the expression of uPAR on monocytes in patients with relapsing-remitting **multiple sclerosis** (RRMS) not currently participating in a clinical trial and in patients with RRMS who were enrolled in a double-blind multicenter clinical trial designed to examine the effect of **glatiramer acetate** (copolymer 1; Copaxone) on relapsing disease. Patients with CPMS have sustained high levels of circulating uPAR-positive (uPAR(+)) monocytes. In comparison, patients with RRMS displayed variable levels of circulating uPAR(+) monocytes. Mean values for uPAR in patients with RRMS were above those seen for controls but were not as high as those observed for patients with secondary progressive MS. Patients with RRMS in the clinical trial also had variable levels of monocyte uPAR. However, patients in the **treatment** group displayed lower levels following 2 years of **treatment**. In both placebo-treated and **glatiramer acetate**-treated patients, the percentage of circulating uPAR(+) monocytes, as well as the density of uPAR expressed per cell (mean linear fluorescence intensity), increased just prior to the onset of a clinically documented exacerbation. Values fell dramatically with the development of clinical symptoms. uPAR levels in all groups correlated with both clinical activity and severity. Results indicate that monocyte activation is impatient in MS and that **glatiramer acetate** may have a significant effect on monocyte activation in patients with RRMS.

L15 ANSWER 30 OF 62 MEDLINE DUPLICATE 12

2001535979 Document Number: 21466757. PubMed ID: 11583066.

Glatiramer acetate in the **treatment** of **multiple sclerosis**. Sela M; Teitelbaum D. (Department of Immunology, Weizmann Institute of Science, Rehovot, Israel.. michael.sela@weizmann.ac.il) . Expert Opin Pharmacother, (2001 Jul) 2 (7) 1149-65. Ref: 79. Journal code: 100897346. ISSN: 1465-6566. Pub. country: England: United Kingdom. Language: English.

AB This review article summarises the initial preclinical studies as well as the different stages of clinical trials in **multiple sclerosis** (MS) with Copolymer 1 (Cop 1), recently denoted **glatiramer acetate**. Experimental studies on **autoimmune** encephalomyelitis (EAE), the animal model of MS, as well as studies on the mechanism of action in both animals and humans are discussed. The review describes the early clinical trials which were followed by Phase II and III trials, culminating in FDA approval in 1996 for the **treatment** of relapsing-remitting MS. The accumulated experience with **glatiramer acetate** indicates that its efficacy is apparently increased as a function of usage time while the favourable side effect profile is sustained. MRI studies revealed that **treatment** with **glatiramer acetate** resulted in a significant reduction of gadolinium (Gd)-enhancing lesions. Ongoing clinical trials which might extend its usage or change its mode of delivery are also described. **Glatiramer acetate**

appears to be a **treatment** of choice for the relapsing-remitting type of MS.

L15 ANSWER 31 OF 62 MEDLINE DUPLICATE 13
2001691491 Document Number: 21600754. PubMed ID: 11735654. Risk-benefit assessment of **glatiramer acetate** in **multiple sclerosis**. Ziemssen T; Neuhaus O; Hohlfeld R. (Department of Neuroimmunology, Max Planck Institute of Neurobiology, Martinsried, Germany.. ziemssen@neuro.mpg.de) . DRUG SAFETY, (2001) 24 (13) 979-90. Journal code: 9002928. ISSN: 0114-5916. Pub. country: New Zealand. Language: English.

AB **Glatiramer acetate**, formerly known as copolymer 1, is a mixture of synthetic polypeptides composed of four amino acids. **Glatiramer acetate** has been shown to be effective in preventing and suppressing experimental **autoimmune** encephalitis (EAE), the animal model of **multiple sclerosis** (MS). Therefore it was tested in several clinical studies, where it was found to slow the progression of disability and to reduce the relapse rate and the magnetic resonance imaging (MRI)-defined disease activity and burden in relapsing-remitting MS. As a daily standard dose, 20mg of **glatiramer acetate** is injected subcutaneously. After injection, **glatiramer acetate** undergoes rapid degradation to amino acids and shorter peptides; so it is not possible to measure any systemic plasma concentrations or excretion rates. Two major mechanisms have been proposed to explain the effects of **glatiramer acetate** in EAE and MS: the induction of **glatiramer acetate**-reactive T helper 2 (Th2)-like regulatory suppressive cells and the interference with T cell activation as an altered peptide ligand. The most common adverse effects were mild injection site reactions (erythema, inflammation and induration). The most remarkable adverse event is the acute and transient immediate postinjection reaction manifested by flushing, chest tightness, palpitations and dyspnoea. Other reported adverse effects are transient chest pain and lymphadenopathy. Antibodies to **glatiramer acetate** induced during **treatment** do not interfere with its clinical effects. In several controlled clinical studies, **glatiramer acetate** has been shown to provide consistent, reproducible clinical benefits in the target population of patients with relapsing-remitting MS. The safety profile and risk-benefit ratio are excellent. Overall, **glatiramer acetate** is very well tolerated and has an excellent risk-benefit profile in patients with relapsing-remitting MS.

L15 ANSWER 32 OF 62 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2003:113391 Document No.: PREV200300113391. Immunotherapy of **multiple sclerosis**: Where are we? Where should we go. Martin, Roland (1); Stuerzebecher, Claus-Steffen; McFarland, Henry F. (1). (1) Neuroimmunology Branch, NINDS, National Institutes of Health, 10 Center DR, Building 10, Room 5B-16, MSC 1400, Bethesda, MD, 20892-1400, USA: martinr@ninds.nih.gov USA. Nature Immunology, (September 2001, 2001) Vol. 2, No. 9, pp. 785-788. print. ISSN: 1529-2908. Language: English.

AB Differences in **multiple sclerosis** patient's disease and their responses to standard drugs indicate that today's therapies need to be more individualized. It is proposed that gene expression profiling in conjunction with magnetic resonance imaging be used to optimize future **treatment** approaches.

L15 ANSWER 33 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)
2001:372819 The Genuine Article (R) Number: 427PN. **Treatment** of **multiple sclerosis** with Copaxone (COP) Elispot assay detects COP-induced interleukin-4 and interferon-gamma response in blood cells. Farina C; Bergh F T; Albrecht H; Meinl E; Yassouridis A; Neuhaus O; Hohlfeld R (Reprint). Univ Munich, Klinikum Grosshadern, Inst Clin Neuroimmunol, Marchioninistr 15, D-81366 Munich, Germany (Reprint); Univ

Munich, Klinikum Grosshadern, Inst Clin Neuroimmunol, D-81366 Munich, Germany; Univ Munich, Klinikum Grosshadern, Dept Neurol, D-81366 Munich, Germany; Max Planck Inst Neurobiol, Dept Neuroimmunol, Martinsried, Germany; Max Planck Inst Psychiat, Dept Stat, D-8000 Munich, Germany; Marianne Strauss Klin, Berg, Germany. BRAIN (APR 2001) Vol. 124, Part 4, pp. 705-719. Publisher: OXFORD UNIV PRESS. GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND. ISSN: 0006-8950. Pub. country: Germany. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Copolymer-1 (Copaxone or COP) inhibits experimental allergic encephalomyelitis and has beneficial effects in **multiple sclerosis**. There is presently no practical in vitro assay for monitoring the immunological effects of COP. We used an automated, computer-assisted enzyme-linked immunoadsorbent spot assay for detecting COP-induced interferon-gamma (IFN-gamma)- and interleukin-4 (IL-4)-producing cells and a standard proliferation assay to assess the immunological response to COP in peripheral blood mononuclear cells from 20 healthy donors, 20 untreated **multiple sclerosis** patients and 20 COP-treated **multiple sclerosis** patients, Compared with untreated acid healthy controls, COP-treated patients showed (i) a significant reduction of COP-induced proliferation; (ii) a positive IL-4 Elispot response mediated predominantly by CD4 cells after stimulation with a wide range of COP concentrations; and (iii) an elevated IFN-gamma response partially mediated by CD8 cells after stimulation with high COP concentrations. All three effects were COP-specific as they were not observed with the control antigens, tuberculin-purified protein or tetanus toroid, The COP-induced changes were consistent over time and allowed correct identification of COP-treated and untreated donors in most cases, We propose that these criteria may be helpful to monitor the immunological response to COP in future clinical trials.

L15 ANSWER 34 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)
2001:287190 The Genuine Article (R) Number: 414ZY. Mechanisms of action of **glatiramer acetate** in **multiple sclerosis**. Neuhaus O; Farina C; Wekerle H; Hohlfeld R (Reprint). Univ Munich, Klinikum Grosshadern, Inst Clin Neuroimmunol, Marchioninistr 15, D-81366 Munich, Germany (Reprint); Max Planck Inst Neurobiol, Dept Neuroimmunol, Martinsried, Germany; Univ Munich, Inst Clin Neuroimmunol, Munich, Germany; Univ Munich, Dept Neurol, Munich, Germany. NEUROLOGY (27 MAR 2001) Vol. 56, No. 6, pp. 702-708. Publisher: LIPPINCOTT WILLIAMS & WILKINS. 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA. ISSN: 0028-3878. Pub. country: Germany. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Glatiramer acetate** (GA, Copaxone [Teva Pharmaceuticals, Kansas City, MO], formerly known as copolymer-1) and interferon- (IFN)-beta are both used for the immunomodulatory **treatment** of **multiple sclerosis**, but they act in different ways. Four major mechanisms of GA have been identified: 1) competition with myelin-basic protein (MBP) for binding to major histocompatibility complex (MHC) molecules; 2) competition of GA/MHC with MBP/MHC for binding to the T-cell receptor; 3) partial activation and tolerance induction of MBP-specific T cells (action as an altered peptide ligand); and 4) induction of GA-reactive T-helper 2- (TH2)-like regulatory cells. Of these four mechanisms, 1 and 2 presumably occur only in vitro and are therefore irrelevant for the in vivo effects of GA. In contrast, mechanisms 3 and 4 could occur in vivo and both could contribute to the clinical effects of GA.

L15 ANSWER 35 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)
2001:727776 The Genuine Article (R) Number: 469XT. Current concepts on the use of immunomodulatory drugs in the **treatment** of **multiple sclerosis**.. Correale J (Reprint); Cristiano E. FLENI, Inst Invest Neurol Dr Raul Carrea, Dept Neurol, Montaneses 2325,

RA-1428 Buenos Aires, DF, Argentina (Reprint); FLENI, Inst Invest Neurol Dr Raul Carrea, Dept Neurol, RA-1428 Buenos Aires, DF, Argentina; Hosp Italiano Buenos Aires, Dept Neurol, Buenos Aires, DF, Argentina. MEDICINA-BUENOS AIRES (AUG 2001) Vol. 61, No. 4, pp. 470-480. Publisher: MEDICINA (BUENOS AIRES). DONATO ALVAREZ 3150, 1427 BUENOS AIRES, ARGENTINA . ISSN: 0025-7680. Pub. country: Argentina. Language: Spanish.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Biotechnological research and a better understanding of the immunopathogenesis of **multiple sclerosis** (MS) have recently led to major breakthroughs in **treatment**. Different drugs that modify the disease process such as interferon beta 1a, interferon beta 1b and **glatiramer acetate** are now available. Decisions about initiation of therapy and choice of agent should be individualised based on the severity and activity of the disease, concomitant illnesses, adverse effects of the drugs, lifestyle issues, and patient preferences. These different drugs were tested in different clinical trials that used different designs, patient populations, endpoints and statistical analysis. Therefore, simple comparisons between them are hazardous. In this article, the pivotal clinical trials of beta interferons and **glatiramer acetate** in the **treatment** of MS are reviewed, and recommendations for their appropriate use are provided. Several ongoing and planned clinical trials in various stages of disease will help to define further the role of these agents in the **treatment** of **multiple sclerosis**.

L15 ANSWER 36 OF 62 MEDLINE
2001456101 Document Number: 21393237. PubMed ID: 11501229.
Glatiramer acetate (Copaxone). Francis D A. (Queen Elizabeth Neuroscience Centre, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH, UK.) INTERNATIONAL JOURNAL OF CLINICAL PRACTICE, (2001 Jul-Aug) 55 (6) 394-8. Ref: 61. Journal code: 9712381. ISSN: 1368-5031. Pub. country: England: United Kingdom. Language: English.

AB **Glatiramer acetate** (Copaxone) is a novel preparation of synthetic peptides composed of four amino acids. Laboratory studies have shown that it prevents, or modifies, experimental allergic encephalomyelitis, the animal model for **multiple sclerosis** (MS), in several mammalian species. Its mode of action has not been fully elucidated but it is known to induce suppresser T-cells, known to be deficient in MS, and competitively inhibits the effect of CNS myelin antigens, thought to be important in the pathogenesis of MS, through MHC blockade. Controlled clinical trials have shown it to improve the natural history of MS by reducing both the relapse rate and the resultant disability. GA shows similar efficacy to interferon-beta (IFN-beta) but with fewer systemic side-effects and appears to be better tolerated by patients. It has thus justified its place in the new era of disease-modifying **treatments** for MS. While the evidence suggests GA should be considered as first-line therapy in selected patients, its differing mechanism of action also gives patients and doctors the option of an alternative agent when the efficacy of IFN-beta is waning or side-effects predominate.

L15 ANSWER 37 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)
2001:694986 The Genuine Article (R) Number: 465QD. **Glatiramer acetate** induces a Th2-biased response and crossreactivity with myelin basic protein in patients with MS. Chen M; Gran B; Costello K; Johnson K; Martin R; Dhib-Jalbut S (Reprint). Univ Maryland Hosp, Dept Neurol, Rm N4W46, 22 S Greene St, Baltimore, MD 21201 USA (Reprint); Univ Maryland, Sch Med, Baltimore, MD 21201 USA; NINDS, Neuroimmunol Branch, NIH, Bethesda, MD 20892 USA; Baltimore VA Med Ctr, Baltimore, MD 21201 USA . MULTIPLE SCLEROSIS (AUG 2001) Vol. 7, No. 4, pp. 209-219. Publisher: ARNOLD, HODDER HEADLINE PLC. 338 EUSTON ROAD, LONDON NW1 3BH, ENGLAND. ISSN: 1352-4585. Pub. country: USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Glatiramer acetate** (GA) is an approved **treatment** for **multiple sclerosis** (MS). The proposed mechanism of action is the induction of GA-specific T cells characterized by protective anti-inflammatory Th2 response. We tested this hypothesis in II MS patients treated with GA from 1 - 19 months. Interferon-gamma and IL-5 (markers of Th1 and Th2 responses respectively) were assayed by ELISA in GA-specific T-cell lines (TCL) supernatants. Th1/Th2 bias was defined based on the ratio of IFN-gamma /IL-5 secretion. Fifty-eight pre-**treatment** and 75 on-**treatment** GA-specific TCL were generated. On-**treatment** mean IL-5 levels in GA-TCL increased significantly, whereas those for IFN-gamma were markedly reduced. Consequently, the ratio of IFN gamma /IL-5 also shifted in favor of a Th2 response. The percentage of GA-TCL classified as Th I was decreased, whereas those classified as TH increased on-**treatment** as compared to pre-**treatment**. Some GA-specific TC (approximately 25%) generated during **treatment** secreted predominantly IL-5 in response to MBP and the immunodominant MBP peptide 83-99, indicating that these crossreactive antigens can act as partial agonists for GA-reactive TCL. These results strongly suggest that the mechanism of action of GA in MS involves the induction of crossreactive GA-specific T cells with a predominant Th2 cytokine profile.

L15 ANSWER 38 OF 62 MEDLINE DUPLICATE 14

2001434880 Document Number: 21182179. PubMed ID: 11285002.

Autoimmune hyperthyroidism in **multiple sclerosis** under **treatment** with **glatiramer acetate**--a case report. Heesen C; Gbadamosi J; Schoser B G; Pohlau D. EUROPEAN JOURNAL OF NEUROLOGY, (2001 Mar) 8 (2) 199. Journal code: 9506311. ISSN: 1351-5101. Pub. country: England: United Kingdom. Language: English.

L15 ANSWER 39 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)

2001:303467 The Genuine Article (R) Number: 419JW. Humoral and cellular immune responses to Copolymer 1 in **multiple sclerosis** patients treated with Copaxone (R). Brenner T; Arnon R; Sela M; Abramsky O; Meiner Z; Riven-Kreitman R; Tarcik N; Teitelbaum D (Reprint). Weizmann Inst Sci, Dept Immunol, IL-76100 Rehovot, Israel (Reprint); Hadassah Univ Hosp, Dept Neurol, IL-91120 Jerusalem, Israel; Teva Pharmaceut, R&D Div, Netanya, Israel. JOURNAL OF NEUROIMMUNOLOGY (2 APR 2001) Vol. 115, No. 1-2, pp. 152-160. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0165-5728. Pub. country: Israel. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Humoral and cellular immune responses were followed in **multiple sclerosis** patients treated with Copolymer 1 (Cop1, **glatiramer acetate**, Copaxone(R)) who participated in three different clinical trials. All patients (130) developed Cop1 reactive antibodies, which peaked at 3 months after initiation of **treatment**, decreasing at 6 months and remaining low. IgG1 antibody levels were 2-3-fold higher than those of IgG2. The proliferative response of Peripheral Blood Mononuclear Cells (PBMC) to Cop1 was initially high and gradually decreased during **treatment**. Antibodies and T cell responses to MBP were low and did not change significantly during the **treatment**. The humoral and cellular immunological responses to Cop1 do not correlate with the side effects and do not affect its therapeutic activity. The preferential production of IgG1 over IgG2 antibodies may indicate that Th2 responses are involved in mediating the clinical effect of Cop1. (C) 2001 Published by Elsevier Science B.V.

L15 ANSWER 40 OF 62 MEDLINE DUPLICATE 15

2001447183 Document Number: 21126505. PubMed ID: 11223159.

Glatiramer acetate blocks interleukin-1-dependent nuclear factor-kappaB activation and RANTES expression in human U-251 MG

astroglial cells. Li Q Q; Bever C T. (Departments of Neurology, University of Maryland School of Medicine, 21201, Baltimore, MD, USA.. qli001@umaryland.edu) . BRAIN RESEARCH. MOLECULAR BRAIN RESEARCH, (2001 Feb 19) 87 (1) 48-60. Journal code: 8908640. ISSN: 0169-328X. Pub. country: Netherlands. Language: English.

AB RANTES is a basic 8-kDa polypeptide of the C-C chemokine subfamily with strong chemoattractant activity for T lymphocytes and monocytes/macrophages that are implicated in the pathogenesis of **multiple sclerosis** (MS) lesions. **Glatiramer acetate** is a drug recently approved for the **treatment** of MS. We therefore investigated the effect of **glatiramer acetate** on RANTES expression in glial cells in vitro. **Treatment** of human U-251 MG astroglial cells with **glatiramer acetate** blocks IL-1beta-induced RANTES chemokine production in a dose- and time-dependent manner. **Glatiramer acetate** also decreased steady-state levels of RANTES mRNA in these cells, which was attributable to reduced transcription, as assessed by nuclear run-on assays. In addition, we showed that NF-kappaB may be the transcriptional activator responsible for the IL-1beta-mediated RANTES gene expression in this system. Our data indicated that the IL-1beta-induced increase in RANTES was associated with an increase in in vitro nuclear extract binding activity specific for the NF-kappaB site in the promoter region of the RANTES gene. The increases in RANTES mRNA and protein expression were suppressed by the NF-kappaB inhibitors gliotoxin, isohelenin, and pyrrolidine dithiocarbamate (PDTC). Furthermore, we demonstrated that the increase in NF-kappaB DNA-binding activity was prevented by pretreatment with **glatiramer acetate** or the NF-kappaB inhibitors. Our results suggest that **glatiramer acetate** may inhibit IL-1beta-stimulated RANTES expression in human glial cells by blocking NF-kappaB activation, thus identifying part of the molecular basis for its anti-inflammatory and immunosuppressive effects in demyelinating diseases.

L15 ANSWER 41 OF 62 MEDLINE

2001459829 Document Number: 21217489. PubMed ID: 11321192. United States open-label **glatiramer acetate** extension trial for relapsing **multiple sclerosis**: MRI and clinical correlates. **Multiple Sclerosis** Study Group and the MRI Analysis Center. Wolinsky J S; Narayana P A; Johnson K P. (Department of Neurology, The University of Texas-Houston, Health Science Center, 77030, USA. (Multiple Sclerosis Study Group and the MRI Analysis Center).) MULTIPLE SCLEROSIS, (2001 Feb) 7 (1) 33-41. Journal code: 9509185. ISSN: 1352-4585. Pub. country: England: United Kingdom. Language: English.

AB After the placebo-controlled extension of the pivotal US trial of **glatiramer acetate** for the **treatment** of relapsing **multiple sclerosis** ended, 208 participants entered an open-label, long-term **treatment** protocol Magnetic resonance imaging (MRI) was added to the planned evaluations of these subjects to determine the consequences of long-term **treatment** on MRI-defined pathology and evaluate its clinical correlates. Of the 147 subjects that remained on long-term follow-up, adequate images were obtained on 135 for quantitative MRI analysis. The initial imaging sessions were performed between June 1998 and January 1999 at 2,447 +/- 61 days (mean +/- standard deviation) after the subject's original randomization. Clinical data from a preplanned clinical visit were matched to MRI within 3 +/- 51 days. At imaging, 66 patients originally randomized to placebo (oPBO) in the pivotal trial had received **glatiramer acetate** for 1,476 +/- 63 days, and 69 randomized to active **treatment** with **glatiramer acetate** (oGA) were on drug for 2,433 +/- 59 days. The number of documented relapses in the 2 years prior to entering the open-label extension was higher in the group originally randomized to placebo (oPBO=1.86 +/- 1.78, oGA=1.03 +/- 1.28; P=0.002). The annualized relapse rate observed during the open-label study

was similar for both groups (oPBO=0.2 7, +/- 0.45 oGA=0.28 +/- 0.40), but the reduction in rate from the placebo-controlled phase was greater for those beginning therapy with GA (oPBO reduced by 0.66 +/- 0.71, oGA reduced by 0.23 +/- 0.58; P=0.0002). One or more gadolinium enhancing lesions were found in 27.4% of all patients (number of distinct enhancements=1.16 +/- 2.52, total enhanced tissue volume=97 +/- 26 microl). The risk of having an enhancement was higher in those with relapses during the open-label extension (odds ratio 4.65, 95% confidence interval (CI) 2.0 to 10.7; P=0.001). The odds for finding an enhancement was 2.5 times higher for those patients originally randomized to placebo (CI 1.1 to 5.4; P=0.02) compared to those always on **glatiramer acetate**. MRI-metrics indicative of chronic pathology, particularly measures of global cerebral tissue loss (atrophy), were uniformly worse for those originally on placebo. These observations enrich our long-term follow up of the clinical consequences of **treatment** with **glatiramer acetate** to include its apparent effects on MRI-defined pathology. They show that the effect of **glatiramer acetate** on enhancements is definite, but modest, consistent with the drug's described mechanisms of action, and that a delay in initiating **treatment** results in progression of MRI-measured pathology that can be prevented.

L15 ANSWER 42 OF 62 MEDLINE DUPLICATE 16
2001557175 Document Number: 21489669. PubMed ID: 11603112. [New approaches in research of therapy of **multiple sclerosis**]. Neue Forschungsansatze zur Therapie der multiplen Sklerose. Hemmer B; Cepok S; Nessler S; Sommer N. (Arbeitsgruppe fur klinische Neuroimmunologie, Neurologische Klinik, Philipps-Universitat Marburg.. hemmer@mailer.uni-marburg.de) . MEDIZINISCHE KLINIK, (2001 Sep 15) 96 Suppl 1 23-8. Journal code: 8303501. ISSN: 0723-5003. Pub. country: Germany: Germany, Federal Republic of. Language: German.

AB BACKGROUND: **Multiple sclerosis** is a chronic inflammatory demyelinating disease of the central nervous system. With a prevalence of 0.1-0.15% in Germany **multiple sclerosis** is the most common cause of severe disability in young adults. PATHOGENESIS: Epidemiological and family studies demonstrate the role of environmental and genetic factors in the pathogenesis of **multiple sclerosis**. Based on those observations and findings in experimental animal models, it is believed that **multiple sclerosis** is caused by an **autoimmune** process. However, target antigens and mechanisms leading to tissue destruction are largely unknown. THERAPY: Since the efficacy of current immunomodulatory and immunosuppressive therapies (beta-interferons, **glatiramer acetate**, mitoxantrone) is limited, it is necessary to develop new strategies for the **treatment** of **multiple sclerosis**. To reach this goal, a much better understanding of disease pathogenesis is necessary which takes into account the clinical, paraclincial and histopathological heterogeneity of the disease. CONCLUSION: Only further intensive research activity on basic mechanisms of disease pathogenesis and a consequent development of resulting therapeutic strategies--from animal models to phase III studies--will result in significant improvement of the long-term course of **multiple sclerosis**.

L15 ANSWER 43 OF 62 CAPLUS COPYRIGHT 2003 ACS
2000:34733 Document No. 132:88184 Inhibitors of the interaction of glutamate with the AMPA and/or kainate receptor complex for **treatment** of demyelinating disorders. Turski, Lechoslaw; Smith, Terence (Eisai Co., Ltd, Japan). PCT Int. Appl. WO 2000001376 A2 20000113, 104 pp. DESIGNATED STATES: W: JP, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB2112 19990702. PRIORITY: GB 1998-14380 19980702; GB 1998-24393 19981106.

AB New therapies can be devised based upon a demonstration of the role of glutamate in the pathogenesis of demyelinating disorders. Inhibitors of the interaction of glutamate with the AMPA and/or kainate receptor complex are likely to be useful in treating demyelinating disorders and can be formulated as pharmaceutical compns.

L15 ANSWER 44 OF 62 MEDLINE DUPLICATE 17
2001022672 Document Number: 20481932. PubMed ID: 11027347. Specific Th2 cells accumulate in the central nervous system of mice protected against experimental **autoimmune** encephalomyelitis by copolymer 1.
Aharoni R; Teitelbaum D; Leitner O; Meshorer A; Sela M; Arnon R. (Departments of Immunology and Biological Services, The Weizmann Institute of Science, Rehovot 76100, Israel.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 Oct 10) 97 (21) 11472-7. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.
AB This study addresses the issue of the effect of immunomodulating therapies in the target organ-the central nervous system (CNS)-in the case of **multiple sclerosis**. Copolymer 1 (Cop 1, Copaxone, **glatiramer acetate**), an approved drug for the **treatment** of **multiple sclerosis**, is a potent inducer of Th2 regulatory cells in both mice and humans. Highly reactive Cop 1-specific T cell lines that secrete IL-4, IL-5, IL-6, IL-10, and transforming growth factor-beta in response to Cop 1 and crossreact with myelin basic protein (MBP) at the level of Th2 cytokine secretion were established from both brains and spinal cords of Cop 1-treated mice. In contrast, no reactivity to the control antigen lysozyme could be obtained in lymphocytes isolated from CNS of mice injected with lysozyme. Adoptively transferred labeled Cop 1-specific suppressor cells were found in brain sections 7 and 10 days after their injection to the periphery, whereas lysozyme-specific cells were absent in the CNS. Hence, Cop 1-induced Th2 cells cross the blood-brain barrier and accumulate in the CNS, where they can be stimulated in situ by MBP and thereby exert therapeutic effects in the diseased organ. This therapeutic effect was manifested, in brains of experimental **autoimmune** encephalomyelitis-induced mice, by a decrease in the inflammatory cytokine interferon-gamma and by secretion of the anti-inflammatory cytokine IL-10 in response to the autoantigen MBP.

L15 ANSWER 45 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)
2000:941620 The Genuine Article (R) Number: 381NY. Mechanisms of immunomodulation by **glatiramer acetate**. Gran B; Tranquill L R; Chen M; Bielekova B; Zhou W; DhibJalbut S; Martin R (Reprint). NINCDS, CELLULAR IMMUNOL SECT, NEUROIMMUNOL BRANCH, NIH, BLDG 10, ROOM 5B-16, 10 CTR DR MSC 1400, BETHESDA, MD 20892 (Reprint); NINCDS, CELLULAR IMMUNOL SECT, NEUROIMMUNOL BRANCH, NIH, BETHESDA, MD 20892; UNIV MARYLAND, SCH MED, DEPT NEUROL, BALTIMORE, MD 21201. NEUROLOGY (12 DEC 2000) Vol. 55, No. 11, pp. 1704-1714. Publisher: LIPPINCOTT WILLIAMS & WILKINS. 530 WALNUT ST, PHILADELPHIA, PA 19106-3621. ISSN: 0028-3878. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Objective: To define the mechanism of action of **glatiramer acetate** (GA; formerly known as copolymer-1) as an immunomodulatory **treatment** for MS. Background: The proposed mechanisms of action of GA include 1) functional inhibition of myelin-reactive T cells by human leukocyte antigen (HLA) blocking, 2) T-cell receptor (TCR) antagonism, and 3) induction of T helper 2 (Th2) immunomodulatory cells. In this report, the authors examined the effects of GA on the functional activation of human T-cell clones (TCC) specific for myelin basic protein (MBP) and for foreign antigens. Several questions were addressed: Is the inhibitory effect of GA specific for autoantigens? Is it mediated by blocking the interaction between peptide and HLA molecule? Is GA a partial agonist or TCR antagonist, or does it induce anergy? Does it induce Th2 modulatory T

cells? Methods: The effects of GA on antigen-induced activation of human TCC specific for MBP, influenza virus hemagglutinin, and Borrelia burgdorferi were studied by proliferation and cytokine measurements, TCR downmodulation, and anergy assays. GA-specific TCC were generated in vitro from the peripheral blood of patients and healthy controls by limiting dilution. Results: GA more strongly inhibited the proliferation of MBP, as compared with foreign antigen-specific TCC; in some MBP-specific TCC, the production of Th1-type cytokines was preferentially inhibited. In addition to HLA competition, the induction of anergy, but not direct TCR antagonism, was observed. Numerous GA-specific TCC were generated from the peripheral blood of both MS patients and normal controls, and a fraction of these showed a Th2 phenotype. Conclusions: This study confirms a preferential inhibitory effect of GA on autoreactive TCC. With respect to cellular mechanisms, although HLA competition appears to play the most important role in functional inhibition in vitro, a direct effect on the TCR may be involved at least in some autoreactive T cells as shown by anergy induction. Although not confirmed at the clonal level, it is demonstrated further that GA induces T cells that crossreact with myelin proteins. GA-specific, Th2-modulatory cells may play an important role in mediating the effect of the drug in vivo.

L15 ANSWER 46 OF 62 MEDLINE DUPLICATE 18
2001102965 Document Number: 20516062. PubMed ID: 11060734. Evaluation of mitoxantrone for the **treatment** of **multiple sclerosis**. Jain K K. (Jain PharmaBiotech, Blasiring 7, CH-4057 Basel, Switzerland.. jain@pharmabiotech.ch) . EXPERT OPINION ON INVESTIGATIONAL DRUGS, (2000 May) 9 (5) 1139-49. Ref: 26. Journal code: 9434197. ISSN: 1354-3784. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Mitoxantrone (Novantrone((R))), an antineoplastic agent, has been approved for treating patients with secondary progressive **multiple sclerosis** (MS). Mitoxantrone, which is usually categorised as an immunosuppressant drug, is now also considered to be a specific immunomodulator. **Autoimmune** mechanism of pathogenesis of MS is the basis of immunosuppressive therapeutic approaches to MS whereas immunoregulatory abnormalities including defective IFN-alpha production provide the rationale for immunomodulating therapies. Clinical trials have shown that mitoxantrone had a statistically significant impact on reduction of relapse rate and delay in disability progression in these patients. Advantages of mitoxantrone as therapy for MS are: (1) considerable information is available about its pharmacokinetics, metabolism and toxicology from previous use in oncology; (2) it requires administration only once in three months which is not only convenient for the patient but also cost-effective; (3) mitoxantrone is one of the two drugs to be approved for secondary progressive MS (the other is IFN-beta1) which offers an advantage over IFN-beta1a preparations and **glatiramer acetate** which are indicated only for relapsing remitting MS. However, the duration of therapy is usually limited to two to three years because the maximum cumulative dose recommended is 120 mg/m(2) due to concern for possible cardiotoxicity. Potential market value of the mitoxantrone, based on the cost of **treatment** per patient and the number of patients likely to be treated in the first year of introduction, is US$210 million.

L15 ANSWER 47 OF 62 MEDLINE DUPLICATE 19
2000236585 Document Number: 20236585. PubMed ID: 10776827. What is new in the **treatment** of **multiple sclerosis**?. Weinstock-Guttman B; Jacobs L D. (Buffalo General Hospital and Baird Center for Multiple Sclerosis at SUNY University, New York 14203, USA.. BWeinstock-Guttman@KaleidaHealth.Org) . DRUGS, (2000 Mar) 59 (3) 401-10. Ref: 43. Journal code: 7600076. ISSN: 0012-6667. Pub. country: New Zealand. Language: English.

AB **Multiple sclerosis** (MS) is considered an

autoimmune disease associated with immune activity directed against central nervous system antigens. Based on this concept, immunosuppression and immunomodualtion have been the mainstays of therapeutic strategies in MS. During the last decade new therapies have been shown to significantly improve MS disease course. The effective therapies have led to a better understanding of MS pathogenesis and further development of even more efficient therapeutic interventions. Recombinant interferon (IFN)beta represents the first breakthrough in MS therapy. Three large placebo-controlled, double-blind studies and several smaller studies have demonstrated the efficacy of different forms of IFNbeta administrated by either subcutaneous or intramuscular routes and at different doses in patients with active relapsing-remitting **multiple sclerosis** (RR-MS). The three IFNbeta drugs are IFNbeta-1b and two IFNbeta-1a preparations (Avonex and Rebif). Although each clinical trial had unique features and differences that make direct comparisons difficult, the aggregate results demonstrate a clear benefit of IFNbeta for decreasing relapses and probability of sustained clinical disability progression in patients with RR-MS. All forms of IFNbeta therapy had beneficial effects on the disease process measured by brain magnetic resonance imaging (MRI). IFNbeta-1a (Avonex) also showed benefit in slowing or preventing the development of MS related brain atrophy measured by MRI after 2 years of therapy. **Glatiramer acetate**, the acetate salt of a mixture synthetic polypeptides thought to mimic the myelin basic protein showed a significant positive results in reducing the relapse rate in patients with RR-MS. Follow up of these patients for approximately 3 years continued to show a beneficial effect on disease relapse rate. Recent MRI data supported the beneficial clinical results seen with **glatiramer acetate** in patients with RR-MS. Recent studies using intravenous immune globulin (IVIG) suggest that IVIG could be effective to some degree in patients with RR-MS. However, there is not enough evidence that IVIG is equivalent to IFNbeta or **glatiramer acetate** in the **treatment** of patients with RR-MS. There have also been recent therapeutical advances in secondary progressive MS (SP-MS). A recent large phase II, placebo-controlled study with IFNbeta-1b in patients with SP-MS convincingly documented that IFNbeta-1b slowed progression of the disease independent of the degree of the clinical disability at the time of **treatment** initiation and independent of presence of superimposed relapses. Mitoxantrone, an anthracenedione synthetic agent, was also shown to be effective as **treatment** for active SP-MS. It is well tolerated but the duration of **treatment** is limited by cumulative cardiotoxicity. There is a growing consensus that disease-modifying therapies should be initiated early in the course of the disease before irreversible clinical disability has developed. Different therapies should be considered and tailored based on patient condition. Combination therapies could be considered as a therapeutic option for patients that failed therapies with IFNbeta and/or **glatiramer acetate**. Currently, there are new ongoing studies testing safety and/or efficacy of different combination regimens (i.e. azathioprine with IFNbeta, IFNbeta with **glatiramer acetate**, or pulses of intravenous cyclophosphamide with IFNbeta). Determining the effect of different therapies on the course of the disease within large clinical studies appears easier than determining individual responsiveness. Therefore, standardised methods for evaluating individual patients receiving disease-modifying therapies and development of effective therapeutic algorithms are needed.

L15 ANSWER 48 OF 62 MEDLINE DUPLICATE 20
2001155758 Document Number: 21079636. PubMed ID: 11212132. Increase in serum levels of uric acid, an endogenous antioxidant, under **treatment** with **glatiramer acetate** for **multiple sclerosis**. Constantinescu C S; Freitag P; Kappos L. (Division of Clinical Neurology, University Hospital, Queen's

Medical Centre, Nottingham, UK.) MULTIPLE SCLEROSIS, (2000 Dec) 6 (6) 378-81. Journal code: 9509185. ISSN: 1352-4585. Pub. country: England: United Kingdom. Language: English.

AB Free radicals including peroxynitrite are induced in **Multiple Sclerosis** (MS). Antioxidant and peroxynitrite inhibitor uric acid (UA), suppresses the MS animal model experimental **autoimmune** encephalomyelitis (EAE). MS patients have lower average serum UA than controls. An inverse relationship exists between MS and gout **Glatiramer acetate** (GA) suppresses EAE and is beneficial in relapsing MS. We investigated serum UA changes during open-label **treatment** of relapsing MS with GAA. Ten patients (six females, four males, aged 19 to 39 years, mean age 32 years) completed 6 months of GAA (Copaxone 20 mg s.c daily). Of these, nine completed 12 months. After 6 months on GAA, serum UA (normal, 173359 micromol/ml for women, 258-491 micromol/ml for men) increased in nine and marginally decreased (302 to 300 micromol/ml) in a single patient. Mean UA significantly increased from 240 to 303 micromol/ml (P=0.0014). At 12 months, UA remained significantly higher than at start (P=0.006) decreasing in only one patient. In contrast, we found no significant UA changes after 6 and 12 months of **treatment** in 21 MS patients treated with interferon beta1-a (Avonex), or in 11 treated with interferon beta1-a (Rebif), or in five placebo-treated controls. Increasing UA, a natural inhibitor of free radicals, may represent a mechanism of action of **glatiramer acetate** in MS.

L15 ANSWER 49 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)

2000:620262 The Genuine Article (R) Number: 342DH. **Glatiramer acetate** (copolymer-1)-specific, human T cell lines: cytokine profile and suppression of T cell lines reactive against myelin basic protein. Dabbert D; Rosner S; Kramer M; Scholl U; Tumani H; Mader M; Weber F (Reprint). UNIV GOTTINGEN, DEPT NEUROL, ROBERT-KOCH-STR 40, D-37075 GOTTINGEN, GERMANY (Reprint); UNIV GOTTINGEN, DEPT NEUROL, D-37075 GOTTINGEN, GERMANY; GERMAN PRIMATE CTR, DEPT VIROL & IMMUNOL, D-37077 GOTTINGEN, GERMANY. NEUROSCIENCE LETTERS (11 AUG 2000) Vol. 289, No. 3, pp. 205-208. Publisher: ELSEVIER SCI IRELAND LTD. CUSTOMER RELATIONS MANAGER, BAY 15, SHANNON INDUSTRIAL ESTATE CO, CLARE, IRELAND. ISSN: 0304-3940. Pub. country: GERMANY. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Glatiramer acetate** (GA), represents an established **treatment** of relapsing/remitting **multiple sclerosis** (MS). The mechanisms responsible for the effect of GA are not fully understood. We generated GA-, myelin basic protein (MBP)- and purified protein derivative (PPD)-specific T cell lines from three MS patients and one healthy donor. The GA-specific lines were CD3(+), CD4(+), CD8(-) and produced tumor-necrosis-factor-alpha (TNF-alpha), interferon-gamma (IFN-gamma), interleukin-4 (IL-4), interleukin-6 (IL-6) and interleukin-10 (IL-10) after stimulation with GA in the presence of irradiated peripheral blood mononuclear cells. MBP-specific T cell lines showed an identical phenotype and secreted TNF-alpha, IFN-gamma, IL-4, IL-10, but not IL-6. Co-culture experiments demonstrated, that GA-specific T cell lines have the capability to suppress the proliferation of MBP-specific T cell lines.

L15 ANSWER 50 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)

2000:587111 The Genuine Article (R) Number: 338WW. Characterization of T cell lines derived from **glatiramer-acetate**-treated **multiple sclerosis** patients. Qin Y F; Zhang D Q; Prat A; Pouly S; Antel J (Reprint). MCGILL UNIV, MONTREAL NEUROL INST, NEUROIMMUNOL UNIT, 3801 UNIV ST, MONTREAL, PQ H3A 2B4, CANADA (Reprint); MCGILL UNIV, MONTREAL NEUROL INST, NEUROIMMUNOL UNIT, MONTREAL, PQ H3A 2B4, CANADA. JOURNAL OF NEUROIMMUNOLOGY (1 AUG 2000) Vol. 108, No. 1-2, pp. 201-206. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE

AMSTERDAM, NETHERLANDS. ISSN: 0165-5728. Pub. country: CANADA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We analyzed the effects of **glatiramer acetate** (GA) therapy on in vitro proliferative responses and cytokine production by lymphocytes derived from **multiple sclerosis** patients receiving this therapy. We confirmed that lymphocytes derived from GA naive patients show a high frequency of response when initially exposed to GA in vitro; this frequency decreased following GA therapy. The frequency of lymphocytes responding to whole MBP stimulation did not change with GA therapy. GA- and MBP-specific T cell lines generated from these patients by repeated cycles of in vitro stimulation did not cross react. Some (23%) whole MBP-reactive T cell lines did cross react with MBP peptide 83-99. The mean levels of interferon (IFN) gamma secretion and the mean ratio of IFN-gamma/lL-5 were lower for GA-reactive cell lines, derived from patients both prior to and during GA therapy, compared to MBP-reactive T cell lines. The proportion of IFN-gamma(+) cells in unfractionated lymphocyte preparations derived from the GA-treated patients did not differ from that found for healthy controls. Our findings indicate that GA-reactive T cell lines derived from GA-treated MS patients continue to show a relative Th2 cytokine bias consistent with a bystander suppressor function. GA **treatment** is not associated with a cytokine phenotype shift in the total T cell or MBP-reactive T cell populations.

L15 ANSWER 51 OF 62 MEDLINE DUPLICATE 21
1999199272 Document Number: 99199272. PubMed ID: 10097125.
Immunomodulation of experimental **autoimmune** encephalomyelitis by oral administration of copolymer 1. Teitelbaum D; Arnon R; Sela M. (Department of Immunology, Weizmann Institute of Science, Rehovot, Israel 76100, USA.. Liteitel@Weizmann.Weizmann.ac.il) . PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Mar 30) 96 (7) 3842-7. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The activity of copolymer 1 (Cop 1, Copaxone, **glatiramer acetate**) in suppressing experimental **autoimmune** encephalomyelitis (EAE) and in the **treatment** of **multiple sclerosis** patients when injected parenterally has been extensively demonstrated. In the present study we addressed the question of whether Cop 1 can induce oral tolerance to EAE similar to myelin basic protein (MBP). We now have demonstrated that oral Cop 1 inhibited EAE induction in both rats and mice. Furthermore, oral Cop 1 was more effective than oral MBP in suppressing EAE in rats. The beneficial effect of oral Cop 1 was found to be associated with specific inhibition of the proliferative and Th1 cytokine secretion responses to MBP of spleen cells from Cop 1-fed mice and rats. In all of these assays, oral Cop 1 was more effective than oral MBP. The tolerance induced by Cop 1 could be adoptively transferred with spleen cells from Cop 1-fed animals. Furthermore, Cop 1-specific T cell lines, which inhibit EAE induction in vivo, could be isolated from the above spleen cells. These T cell lines secrete the anti-inflammatory cytokines IL-10 and transforming growth factor type beta, but not IL-4, in response to both Cop 1 and MBP. In conclusion, oral Cop 1 has a beneficial effect on the development of EAE that is associated with down-regulation of T cell immune responses to MBP and is mediated by Th2/3 type regulatory cells. These results suggest that oral administration of Cop 1 may modulate **multiple sclerosis** as well.

L15 ANSWER 52 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)
1999:892665 The Genuine Article (R) Number: 255VM. Therapeutic strategies in **multiple sclerosis**. I. Immunotherapy. Hohlfeld R (Reprint). UNIV MUNICH, KLINIKUM GROSSHADERN, INST CLIN NEUROIMMUNOL, MARCHIONINISTR 15, D-81366 MUNICH, GERMANY (Reprint); UNIV MUNICH, KLINIKUM GROSSHADERN, DEPT NEUROL, D-81366 MUNICH, GERMANY; MAX PLANCK

INST NEUROBIOL, DEPT NEUROIMMUNOL, D-82152 PLANEGG, GERMANY. PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY OF LONDON SERIES B-BIOLOGICAL SCIENCES (29 OCT 1999) Vol. 354, No. 1390, pp. 1697-1710. Publisher: ROYAL SOC LONDON. 6 CARLTON HOUSE TERRACE, LONDON SW1Y 5AG, ENGLAND. ISSN: 0962-8436 . Pub. country: GERMANY. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB This review first addresses several general aspects of the immunotherapy of **multiple sclerosis**. Next, two approved immunomodulatory **treatments**, interferon-beta and copolymer-1 (**glatiramer acetate**), are reviewed in more detail. Finally, other immunosuppressive therapies and experimental strategies are briefly discussed.

L15 ANSWER 53 OF 62 MEDLINE DUPLICATE 22
1999401238 Document Number: 99401238. PubMed ID: 10472018.
Multiple sclerosis and its **treatment**.
Giovannoni G; Miller D H. (Department of Clinical Neurosciences, Royal Free and University College Medical School, London.. g.giovannoni@rfhsm.ac.uk) . JOURNAL OF THE ROYAL COLLEGE OF PHYSICIANS OF LONDON, (1999 Jul-Aug) 33 (4) 315-22. Ref: 41. Journal code: 7503108. ISSN: 0035-8819. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Multiple sclerosis** (MS) is a common neurological disorder responsible for substantial neurological morbidity. Although it is considered to be an **autoimmune** demyelinating disease of the central nervous system (CNS), mediated by antigen-specific CD4+ T helper (Th1) T-cells, therapeutic strategies aimed at generalised immunosuppression have been disappointing. Recently, immunomodulatory therapies like interferon (IFN)-beta and **glatiramer acetate** have proved more effective. They reduce the rate and severity of clinical relapses and, in the case of IFN-beta, delay the rate of disease progression. Symptomatic therapies and rehabilitation, however, remain the mainstay of **treatment** for the majority of patients with MS. The immunopathogenesis of MS and its **treatments**, both disease modifying and symptomatic, are reviewed below.

L15 ANSWER 54 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)
1999:197101 The Genuine Article (R) Number: 172LV. Disease modifying **treatments** for **multiple sclerosis** - What is on the horizon?. Weilbach F X (Reprint); Gold R. UNIV WURZBURG, NEUROL KLIN, CLIN RES GRP MULTIPLE SCLEROSIS & NEUROMIMMUNOL, DEPT NEUROL, D-97080 WURZBURG, GERMANY (Reprint). CNS DRUGS (FEB 1999) Vol. 11, No. 2, pp. 133-157. Publisher: ADIS INTERNATIONAL LTD. 41 CENTORIAN DR, PRIVATE BAG 65901, MAIRANGI BAY, AUCKLAND 10, NEW ZEALAND. ISSN: 1172-7047. Pub. country: GERMANY. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Stimulated by the successful introduction of interferon-beta as **treatment** for relapsing-remitting **multiple sclerosis** (MS) and based on an improved knowledge of the immunopathology of MS, a vast array of **treatment** options is currently under investigation for disease course modification. These are targeting relapse duration and intensity, relapse rate, disease progression and remyelination. The different approaches comprise mostly recombinant biotechnical agents, but also conventional immunosuppressants.

Interferon-beta now can be regarded as an established disease modifying agent in relapsing remitting and secondary progressive RIS as shown unequivocally in several well designed studies conducted by different pharmaceutical companies. **Glatiramer acetate** is also effective in relapsing remitting MS, although this conclusion is based on a lower level of evidence. A recent positive trial of mitoxantrone in chronic progressive MS underlines the efficacy Of immunosuppression at least in subgroups of patients with MS who have high disease activity.

Aside from the therapeutic approaches now already introduced into the clinical armamentarium. newer agents and **treatment** concepts

include monoclonal antibodies, intravenous immunoglobulins, modulators of trimolecular complex and agents that interact with costimulatory molecules. Cytokine modulators and inhibitors of cell adhesion are promising candidates but their effect on the disturbed immunological network associated with MS has to be investigated thoroughly. In the future, simultaneous or sequential combinations of agents with different targets map significantly improve the efficacy of **treatments** for MS. The clinical evaluation of new **treatment** approaches will he difficult given the hetoregeneity and unpredictable course of the disorder.

Interesting future therapeutic approaches include intracellular signal transduction modulators, vitamins and newer immunosuppressants. Gene therapy, vaccination with naked DNA or dendritic cells may also turn out to be useful. Besides developing new immunotherapies it seems indispensable to improve delivery of symptomatic **treatment** and rehabilitation aiming st the quality of life of individual MS patients. Identification of disease course predictors or **treatment** response a ill improve accuracy of therapeutic decision making.

L15 ANSWER 55 OF 62 MEDLINE
1999080668 Document Number: 99080668. PubMed ID: 9863300. [**Treatment** of **multiple sclerosis**--1. New drugs may be effective but there still are frequent relapses]. Behandling av multipel skleros--1. Nya lakemedel ger lindring vid tata skov. Svenningsson A; Andersson M; Olsson T. (Neurologiska kliniken, Karolinska sjukhuset, Stockholm.) LAKARTIDNINGEN, (1998 Dec 2) 95 (49) 5623-7, 5630. Ref: 19. Journal code: 0027707. ISSN: 0023-7205. Pub. country: Sweden. Language: Swedish.

AB **Multiple sclerosis** (MS) is a demyelinating, central nervous system disease, of putative **autoimmune** pathogenesis. Although no effective pharmacological therapy has been available for this often disabling disease until recently, several studies have now confirmed that subcutaneous or intramuscular administration of beta-interferon may reduce the frequency and severity of relapses in relapsing MS, and may also inhibit disease progression. Studies are under way to determine the possible efficacy of beta-interferon during the progressive phase of the disease. Three beta-interferon formulations are currently available in Sweden. Another drug, **glatiramer acetate**, also shown to have some effect on the disease course, is expected to be registered for use in Sweden shortly.

L15 ANSWER 56 OF 62 CAPLUS COPYRIGHT 2003 ACS
1998:505428 Document No. 129:131047 **Glatiramer acetate**. New mode of action in **multiple sclerosis** therapy. Hellwig, Bettina (Stuttgart, Germany). Deutsche Apotheker Zeitung, 138(32), 2978-2980 (German) 1998. CODEN: DAZEA2. ISSN: 0011-9857. Publisher: Deutscher Apotheker Verlag.

AB The drug **glatiramer acetate** for the **treatment** of **multiple sclerosis** (MS) is presented including MS - an **autoimmune** disease, therapy of MS, efficacy of **glatiramer acetate**, beta-interferon or **glatiramer acetate**, and side effects.

L15 ANSWER 57 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)
1998:850346 The Genuine Article (R) Number: 133WW. Choosing drug therapy for **multiple sclerosis** - An update. vanOosten B W (Reprint); Truyen L; Barkhof F; Polman C H. FREE UNIV AMSTERDAM HOSP, DEPT NEUROL, POB 7057, NL-1007 MB AMSTERDAM, NETHERLANDS (Reprint); FREE UNIV AMSTERDAM HOSP, DEPT DIAGNOST RADIOL, DUTCH MR CTR MS RES, NL-1007 MB AMSTERDAM, NETHERLANDS. DRUGS (OCT 1998) Vol. 56, No. 4, pp. 555-569. Publisher: ADIS INTERNATIONAL LTD. 41 CENTORIAN DR, PRIVATE BAG 65901, MAIRANGI BAY, AUCKLAND 10, NEW ZEALAND. ISSN: 0012-6667. Pub. country: NETHERLANDS. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Multiple sclerosis** (MS) is an immunologically mediated disorder in which inflammation and demyelination of the central nervous system white matter are prominent features, resulting in various neurological signs and symptoms. In most patients, the course of the disease is initially characterised by relapses and remissions. In patients with chronic disease there is a tendency towards a gradually progressive disease course.

MS relapses can best be treated with a course of high dose intravenous methylprednisolone.

In ambulatory patients with relapsing remitting MS, partial prevention of relapses can be achieved by the use of interferon-beta-1a or -1b, whereas there is (as yet less convincing) evidence that **glatiramer acetate** (copolymer-1) might also be effective.

At this time, there is no proof that these drugs are effective in patients with progressive MS, although trial results are expected to be available soon. In patients with rapidly progressive disease, it might be worth considering the effect of methotrexate.

Future **treatment** options include new strategies to interfere with disease-relevant, specific or nonspecific immune mechanisms as well as drugs that might promote remyelination.

In spite of the advances that have been made over the past few years, symptomatic **treatment**, including a multidisciplinary rehabilitation approach, remains the mainstay of **treatment** of the majority of MS patients.

L15 ANSWER 58 OF 62 SCISEARCH COPYRIGHT 2003 ISI (R)

1999:64413 The Genuine Article (R) Number: 155KJ. **Treatment** of **multiple sclerosis** with Copolymer-1 (Copaxone(R)): implicating mechanisms of Th1 to Th2/Th3 immune-deviation. Miller A (Reprint); Shapiro S; Gershtein R; Kinarty A; Rawashdeh H; Honigman S; Lahat N. LADY DAVIS CARMEL MED CTR, NEUROIMMUNOL RES UNIT, 7 MICHAL ST, IL-34362 HAIFA, ISRAEL (Reprint); LADY DAVIS CARMEL MED CTR, MULTIPLE SCLEROSIS CTR, IL-34362 HAIFA, ISRAEL; LADY DAVIS CARMEL MED CTR, DEPT NEUROL, IL-34362 HAIFA, ISRAEL; TECHNION ISRAEL INST TECHNOL, FAC MED, HAIFA, ISRAEL; TECHNION ISRAEL INST TECHNOL, RAPPAPORT INST RES MED SCI, HAIFA, ISRAEL; LADY DAVIS CARMEL MED CTR, MOL IMMUNOL RES UNIT, IL-34362 HAIFA, ISRAEL. JOURNAL OF NEUROIMMUNOLOGY (1 DEC 1998) Vol. 92, No. 1-2, pp. 113-121. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0165-5728. Pub. country: ISRAEL. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The synthetic polypeptide copolymer-1 (Cop-1; Copaxone(R); **Glatiramer Acetate**) has been recently approved as an effective **treatment** in relapsing **multiple sclerosis** (MS). A large body of evidence demonstrates that Cop-1 induces active suppression of CNS-inflammatory disease in animal models. However, Cop-1-mediated suppressor mechanisms have not yet been elucidated in humans. A 12-month open study following clinical and immunological parameters of ten relapsing MS patients treated with Cop-1 is presented. Relapse rates and disability scores (EDSS) were evaluated prior to and after 12 months of **treatment**. The immunological parameters assessed prior to and at 3 months' interval during **treatment** included serum levels of soluble IL-2 receptor (sIL-2R) and IL-IO as well as leukocyte cytokine mRNA expression of TNF alpha, IL-4 and TCF-beta. Copaxone **treatment** was found to lead to a significant reduction in the mean annual relapse rate (from 1.4 prior to **treatment** to 0.6 during **treatment**) and stabilization of disability in 90% of the patients. The **treatment** was accompanied by an elevation of serum IL-10 levels, suppression of the pro-inflammatory cytokine TNF alpha mRNA, and an elevation of the anti-inflammatory cytokines TGF-beta and IL-4 mRNAs in PBLs. These results suggest that the beneficial clinical effects of Copaxone in MS patients may be attributed to changes in

activation of T cell subsets and a shift from Th1 to Th2/Th3 cytokine profile, probably leading to Cop-1-driven mechanisms of bystander suppression. (C) 1998 Elsevier Science B.V. All rights reserved.

L15 ANSWER 59 OF 62 MEDLINE DUPLICATE 23
1998214393 Document Number: 98214393. PubMed ID: 9553777. Current immunotherapy in **multiple sclerosis**. Bashir K; Whitaker J N. (Department of Neurology, University of Alabama at Birmingham 35233-7340, USA.) IMMUNOLOGY AND CELL BIOLOGY, (1998 Feb) 76 (1) 55-64. Ref: 90. Journal code: 8706300. ISSN: 0818-9641. Pub. country: Australia. Language: English.

AB The underlying pathophysiology of **multiple sclerosis** is presumed to be **autoimmune** in nature. Attempts to find an effective **treatment** for this common disease of the central nervous system have primarily focused on immune-mediated therapies, both immunosuppressive and immunomodulatory. The wide variety of immunological abnormalities detected in **multiple sclerosis** and its animal model, experimental allergic encephalomyelitis, has prompted the testing of a diverse array of drugs to be used for **treatment**. Recent successes in the **treatment** of relapsing-remitting **multiple sclerosis** with interferon beta and **glatiramer acetate** have renewed interest in and raised expectations for the effective control of this neurological disorder. Improved methodology in clinical trials, the development of surrogate markers and the availability of novel therapies bode well for more rapid advances.

L15 ANSWER 60 OF 62 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
1999000617 EMBASE Intravenous immunoglobulins in **multiple sclerosis**. Lisak R.P.. Dr. R.P. Lisak, Department of Neurology, University Health Center, 4201 St. Antoine, Detroit, MI 48201, United States. Neurology 51/6 SUPPL. 5 (S25-S29) 1998.
Refs: 42.
ISSN: 0028-3878. CODEN: NEURAI. Pub. Country: United States. Language: English. Summary Language: English.

AB The spectrum of diseases being treated with intravenous immunoglobulins (IVIg) appears to be ever broadening, including use in neurologic diseases. After a period of anectodal reports and smaller uncontrolled series, recently there have been several randomized, prospective, double-blind, placebo- controlled studies employing IVIg in patients with relapsing remitting (RR) **multiple sclerosis** (MS). Reduction in relapse rate and some evidence of decreased MRI activity has been reported, but to date no effect on disability or MRI lesion burden has been noted. Because of differences in methodologic design and patient populations, as well as the relatively small number of patients in some of these studies, a rigorous direct comparison of efficacy with the type I interferons and **glatiramer acetate** is not possible. Given these data and the high cost of IVIg, routine use of this mode of therapy cannot be recommended, certainly not as a first-line **treatment**. Larger studies would clearly be helpful. At present there is no evidence to support the use of IVIg in secondary progressive (SP) or primary progressive (PP) MS.

L15 ANSWER 61 OF 62 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 24
97351868 EMBASE Document No.: 1997351868. Antigen-specific therapies for the **treatment** of **multiple sclerosis**: A clinical trial update. Spack E.G.. E.G. Spack, Department of Immunology, Anergen Inc., 301 Penobscot Drive, Redwood City, CA 94063, United States. Expert Opinion on Investigational Drugs 6/11 (1715-1727) 1997.
Refs: 75.
ISSN: 1354-3784. CODEN: EOIDER. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Within the past year a host of antigen-specific therapies for

multiple sclerosis (MS) progressed along the path from IND submission to FDA approval. The Immune Response Corp. vaccinated patients with a V.beta.6 peptide, demonstrating that the vaccine was immunogenic, well-tolerated and reduced the number of V.beta.6+ T-cells in the cerebrospinal fluid (CSF). Connetics conducted a Phase I/II trial on chronic progressive MS patients vaccinated with CDR2 peptides from TCR V.beta.55.2 and found that patients with a measurable response to the vaccine remained clinically stable for a year. A study at the University of Alberta MS Patient Care and Research Clinic demonstrated that it. injection of a B-cell/T-cell epitope of myelin basic protein (MBP) decreased the level of anti-MBP antibody, but iv. administration did not decrease the relapse rate. **AutoImmune** completed a Phase III trial of oral myelin in the spring of 1997 which failed to show a statistical difference between those patients fed placebo and those fed daily capsules of myelin protein (Myoral). Three Phase I trials of iv. myelin antigen(s) were initiated: MP4 (Alexion Pharmaceuticals), a recombinant fusion of myelin basic protein and proteolipid protein; AG284 (Anergen), a solubilised HLA-DR2:MBP peptide complex; and NBI-5788 (Neurocrine Biosciences), an altered peptide ligand of an immunodominant MBP T-cell epitope. Following the conclusion of a successful Phase III clinical trial, TEVA Pharmaceutical Industries received FDA approval to market Copaxone (**glatiramer acetate**) for the **treatment** of relapsing-remitting MS in December of 1996 and launched the product in 1997. The recent preclinical research and clinical trial status of these antigen-specific MS therapeutics are summarised in this review.

L15 ANSWER 62 OF 62 CAPLUS COPYRIGHT 2003 ACS
1997:333270 Document No. 127:106 Copolymer 1 (Copaxone) from an idea to a drug for **treatment** of **multiple sclerosis**.
Tarcic, Nora; Riven-Kreitman, Rivka (Israel). Kimiya, Handasa Kimit, 28, 14, 16-18 (Hebrew) 1997. CODEN: KHKIEZ. ISSN: 0792-609X. Publisher: S.N.ER.

AB A review with no refs. Copaxone (Copolymer 1, **glatiramer acetate**) is a mixt. of synthetic polypeptides prepd. by the copolymn. of the activated and protected N-carboxyanhydrides of L-alanine, L-glutamic acid, L-lysine and L-tyrosine in a specified ratio. The rigorously controlled prodn. process and a battery of chem., phys., biol. and microbiol. QC assays assure batch-to-batch reproducibility. It was initially researched at the Weizmann Institute of Science in Israel by M. Sela, R. Arnon, D. Teitelbaum and their colleagues, and then developed as a com. drug by TEVA Pharmac. Ind. Ltd. Copolymer-1 has a marked suppressive and preventive effect on exptl. allergic encephalomyelitis (EAE), an animal model for MS. Two complementary mechanisms were proposed for its therapeutic effect: induction of specific suppressor T cells, and interference with auto-antigen presentation. The efficacy of Copaxone in MS was confirmed in 2 independent studies, the most recent of which was a multicenter, placebo-controlled, double blind phase III trial in 251 relapsing MS patients. Copaxone reduced significantly the frequency of relapses and slowed progression of disability. The clin. efficacy was most pronounced in less disabled patients, and was maintained, and even enhanced, with prolonged **treatment**. Copaxone was found to be a safe and well tolerated **treatment**. This has been confirmed in an extensive open clin. trial program in which over 1,500 patients received daily **treatment**. These results show that Copaxone is a safe and effective drug for relapsing MS patients. Copaxone has been recently approved for marketing in Israel and in the USA.

=> s l7 and hemolytic anemia
L16 0 L7 AND HEMOLYTIC ANEMIA

=> s l7 and oophoritis

L17 0 L7 AND OOPHORITIS

=> s l7 and thyroiditis
L18 0 L7 AND THYROIDITIS

=> s l7 and uveoretinitis
L19 0 L7 AND UVEORETINITIS

=> s l7 and crohn's disease
MISMATCHED QUOTE 'CROHN'S'
Quotation marks (or apostrophes) must be used in pairs,
one before and one after the expression you are setting
off or masking.

=> s l7 and crohn disease
L20 0 L7 AND CROHN DISEASE

=> s l7 and "crohn's disease"
L21 0 L7 AND "CROHN'S DISEASE"

=> s l7 and thromocytopenic purpura
L22 0 L7 AND THROMOCYTOPENIC PURPURA

=> s l7 and colitis
L23 0 L7 AND COLITIS

=> s l23 and allergy
L24 0 L23 AND ALLERGY

=> s l7 and contact sensitivity
L25 0 L7 AND CONTACT SENSITIVITY

=> s l7 and diabetes mellitus
L26 0 L7 AND DIABETES MELLITUS

=> s l7 and Graves disease
L27 1 L7 AND GRAVES DISEASE

=> d l27 cbib abs

L27 ANSWER 1 OF 1 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
2001130513 EMBASE **Autoimmune** hyperthyroidism in multiple sclerosis under **treatment** with **glatiramer acetate** - A case report [2]. Heesen C.; Gbadamosi J.; Schoser B.-G.-H.; Pohlau D.. C. Heesen, Department of Neurology, University of Hamburg, Martinistr. 52, D-20246 Hamburg, Germany. heesen@uke.uni-hamburg.de. European Journal of Neurology 8/2 (199) 2001.
Refs: 10.
ISSN: 1351-5101. CODEN: EJNEFL. Pub. Country: United Kingdom. Language: English.

=> s l7 and "Guillain Barre's syndrome"
L28 0 L7 AND "GUILLAIN BARRE'S SYNDROME"

=> s l7 and "Hashimoto's disease"
L29 0 L7 AND "HASHIMOTO'S DISEASE"

=> s l7 and idiopathic myxedema
L30 0 L7 AND IDIOPATHIC MYXEDEMA

=> s l7 and myasthenia gravis
L31 0 L7 AND MYASTHENIA GRAVIS

=> s l7 and psoriasis
L32 1 L7 AND PSORIASIS

=> d l32 cbib abs

L32 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
2001:833075 Document No. 135:367223 Method of treating immune pathologies with low dose estrogen. Offner, Halina (Oregon Health Sciences University, USA; The Government of the United States of America). PCT Int. Appl. WO 2001085154 A2 20011115, 107 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US40710 20010511. PRIORITY: US 2000-PV203980 20000512.
AB The invention provides a method of ameliorating a Th1-mediated immune pathol. in a mammal. The method is practiced by administering a low dose of estrogen to the mammal. Optionally, an immunotherapeutic agent can also be administered to the mammal. Also provided are kits contg. a low dose of estrogen and an immunotherapeutic agent. The immunomodulatory agent is a cytokine or a peptide selected from the group consisting of an antigen peptide, an HLA peptide, a T cell receptor peptide or an analog of any of these peptides.

=> s l7 and pemphigus vulgaris
L33 0 L7 AND PEMPHIGUS VULGARIS

=> s l7 and systemic lupus erythematosus
L34 0 L7 AND SYSTEMIC LUPUS ERYTHEMATOSUS

=> s l7 and GVHD
L35 0 L7 AND GVHD

=> s l7 adn graft versus host disease
MISSING OPERATOR L7 ADN
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l7 and graft versus host disease
L36 0 L7 AND GRAFT VERSUS HOST DISEASE

=> s l7 adn delayed type hypersensitivity
MISSING OPERATOR L7 ADN
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l7 and delayed type hypersensitivity
L37 1 L7 AND DELAYED TYPE HYPERSENSITIVITY

=> d l37 cbib abs

L37 ANSWER 1 OF 1 SCISEARCH COPYRIGHT 2003 ISI (R)
2002:825012 The Genuine Article (R) Number: 600GG. **Treatment** of multiple sclerosis with the pregnancy hormone estriol. Sicotte N L; Liva S M; Klutch R; Pfeiffer P; Bouvier S; Odesa S; Wu T C J; Voskuhl R R (Reprint). Univ Calif Los Angeles, Reed Neurol Res Ctr, Dept Neurol, 710 Westwood Plaza, Los Angeles, CA 90095 USA (Reprint); Univ Calif Los

Angeles, Reed Neurol Res Ctr, Dept Neurol, Los Angeles, CA 90095 USA; Univ Calif Los Angeles, Hlth Sci Ctr, Dept Obstet & Gynecol, Los Angeles, CA 90095 USA. ANNALS OF NEUROLOGY (OCT 2002) Vol. 52, No. 4, pp. 421-428. Publisher: WILEY-LISS. DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012 USA. ISSN: 0364-5134. Pub. country: USA. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Multiple sclerosis patients who become pregnant experience a significant decrease in relapses that may be mediated by a shift in immune responses from T helper I to T,helper 2. Animal models of multiple sclerosis have shown that the pregnancy hormone, estriol, can ameliorate disease and can cause an immune shift. We treated nonpregnant female multiple sclerosis patients with the pregnancy hormone estriol in an attempt to recapitulate the beneficial effect of pregnancy. As compared with pretreatment baseline, relapsing remitting patients treated with oral estriol (8mg/day) demonstrated significant decreases in **delayed type hypersensitivity** responses to tetanus, interferon-gamma levels in peripheral blood mononuclear cells, and gadolinium enhancing lesion numbers and volumes on monthly cerebral magnetic resonance images. When estriol **treatment** was stopped, enhancing lesions increased to pretreatment levels. When estriol. **treatment** was reinstituted, enhancing lesions again were significantly decreased. Based on these results, a larger, placebo-controlled trial of estriol is warranted in women with relapsing remitting multiple sclerosis. This novel **treatment** strategy of using pregnancy doses of estriol in multiple sclerosis has relevance to other **autoimmune** diseases that also improve during pregnancy.

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=> s (gad a?/au or Lis d?/au)
L38        1016 (GAD A?/AU OR LIS D?/AU)

=> s l38 and glatiramer acetate derivative
L39           0 L38 AND GLATIRAMER ACETATE DERIVATIVE

=> s l38 and copolymer 1
L40           4 L38 AND COPOLYMER 1

=> dup remove l40
PROCESSING COMPLETED FOR L40
L41           3 DUP REMOVE L40 (1 DUPLICATE REMOVED)

=> d l41 1-3 cbib abs

L41  ANSWER 1 OF 3  BIOSIS  COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2003:129777  Document No.: PREV200300129777. Copolymer 1
     related polypeptides for use as molecular weight markers and for
     therapeutic use. Gad, Alexander (1); Lis, Dora. (1)
     Nes Ziona, Israel Israel. ASSIGNEE: Yeda Research and Development Co. Ltd.
     at the Weizmann Institute of Science, Israel. Patent Info.: US 6514938
     February 04, 2003. Official Gazette of the United States Patent and
     Trademark Office Patents, (Feb. 4 2003) Vol. 1267, No. 1, pp. No
     Pagination. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN:
     0098-1133. Language: English.
AB   The present invention provides molecular weight markers for accurate
     determination of the molecular weight of glatiramer acetate and other
     copolymers. The present invention further provides a plurality of
     molecular weight markers for determining the molecular weight of
     glatiramer acetate and other copolymers which display linear relationships
     between molar ellipticity and molecular weight, and between retention time
     and the log of the molecular weight. The molecular weight markers also
     optimally demonstrate biological activity similar to glatiramer acetate or
     corresponding copolymers and can be used for treating or preventing
     various immune diseases. In addition, the subject invention provides
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pharmaceutical compositions for the treatment of immune diseases comprising a polypeptide having an identified molecular weight and an amino acid composition corresponding to glatiramer acetate or a terpolymer.

L41 ANSWER 2 OF 3 MEDLINE DUPLICATE 1

2002386520 Document Number: 22129976. PubMed ID: 12134954. Regional peptide uptake study in the rat intestinal mucosa: glatiramer acetate as a model drug. Haupt Susan; Gil Efrat; Tirosh Regin; Klinger Ety; **Gad Alexander**; Rubinstein Abraham. (The Hebrew University of Jerusalem, Faculty of Medicine, School of Pharmacy, Israel.) PHARMACEUTICAL RESEARCH, (2002 Jun) 19 (6) 832-7. Journal code: 8406521. ISSN: 0724-8741. Pub. country: United States. Language: English.

AB PURPOSE: To identify regions of the rat intestine that are able to internalize from the lumen oligopeptides, using the model drug glatiramer acetate (GA). METHODS: GA was introduced into rat intestinal sacs and the integrity of GA during uptake was monitored using antibody detection. Sodium docecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblotting of intestinal homogenates that had been exposed to GA were performed to identify GA presence. An enzyme-linked immunosorbent assay (ELISA) protocol was adapted for GA quantification. Immunohistochemistry was undertaken to examine the rat colonic wall for GA uptake, and confocal microscopy was used to differentiate adsorbed and internalized peptide in cultured colorectal adenocarcinoma cells. RESULTS: The colon and the ileum, respectively, were identified to be the intestinal regions in which GA was maximally preserved during uptake from the lumen. GA was identified to cross the colonic wall from the epithelium to the serosa. Internalization of GA into cultured colonic epithelial cells was demonstrated. CONCLUSIONS: The rat colonic wall was identified to be less proteolytically active toward GA compared to the wall of the more proximal regions of the small intestine. GA has the capacity to penetrate from the lumen into the colonic wall. The maintenance of GA integrity within the wall of the colon offers the potential for local biological activity of the drug.

L41 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS

2000:227679 Document No. 132:264109 **Copolymer 1** related polypeptides for use as molecular weight markers and for therapeutic use. **Gad, Alexander; Lis, Dora** (Yeda Research and Development Co., Ltd., Israel; Teva Pharmaceuticals USA, Inc.). PCT Int. Appl. WO 2000018794 A1 20000406, 72 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US22402 19990924. PRIORITY: US 1998-101693 19980925.

AB The **copolymer 1** related polypeptides are capable of binding to HMC class II antigen, HLA-DR1, HLA-DR2, HLA-DR4, or antigen presenting cell. The **copolymer 1** related polypeptides are useful as mol. wt. markers for accurate detn. of the mol. wt. of glatiramer acetate and other copolymers. The present invention provides a plurality of mol. wt. markers for detg. the mol. wt. of glatiramer acetate and other copolymers which display linear relationships between molar ellipticity and mol. wt., and between retention time and the log of the mol. wt. The mol. wt. markers also optimally demonstrate biol. activity similar to glatiramer acetate or corresponding copolymers and can be used for treating or preventing various immune diseases.

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L42 1 L38 AND GLAT COPOLYMER

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L42 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
2000:227679 Document No. 132:264109 Copolymer 1 related polypeptides for use as molecular weight markers and for therapeutic use. **Gad, Alexander; Lis, Dora** (Yeda Research and Development Co., Ltd., Israel; Teva Pharmaceuticals USA, Inc.). PCT Int. Appl. WO 2000018794 A1 20000406, 72 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US22402 19990924. PRIORITY: US 1998-101693 19980925.
AB The copolymer 1 related polypeptides are capable of binding to HMC class II antigen, HLA-DR1, HLA-DR2, HLA-DR4, or antigen presenting cell. The copolymer 1 related polypeptides are useful as mol. wt. markers for accurate detn. of the mol. wt. of glatiramer acetate and other copolymers. The present invention provides a plurality of mol. wt. markers for detg. the mol. wt. of glatiramer acetate and other copolymers which display linear relationships between molar ellipticity and mol. wt., and between retention time and the log of the mol. wt. The mol. wt. markers also optimally demonstrate biol. activity similar to glatiramer acetate or corresponding copolymers and can be used for treating or preventing various immune diseases.

=> s l38 and TV marker
L43 0 L38 AND TV MARKER

=> s autoimmune disease model
4 FILES SEARCHED...
L44 449 AUTOIMMUNE DISEASE MODEL

=> s l44 and EAE
L45 71 L44 AND EAE

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PROCESSING COMPLETED FOR L45
L46 22 DUP REMOVE L45 (49 DUPLICATES REMOVED)

=> d l46 1-22 cbib abs

L46 ANSWER 1 OF 22 MEDLINE DUPLICATE 1
2002657660 Document Number: 22305113. PubMed ID: 12417437. Semliki Forest virus infection is enhanced in Th1-prone SJL mice but not in Th2-prone BALB/c mice during Linomide-induced immunomodulation. Peltoniemi J; Setala N; Broberg E; Roytta M; Hukkanen V; Salmi A A; Eralinna J-P. (Department of Virology, University of Turku, Kiinamyllynkatu 13, 20520, Turku, Finland.. jutta.peltoniemi@utu.fi) . JOURNAL OF NEUROIMMUNOLOGY, (2002 Nov) 132 (1-2) 83-92. Journal code: 8109498. ISSN: 0165-5728. Pub. country: Netherlands. Language: English.
AB Linomide (quinoline-3-carboxamide) is an immunomodulator with diverse effects on the immune system. Its beneficial effects on experimental

autoimmune disease models have been linked to downregulation of Th1 cytokines and altered macrophage functions. We studied this effect of downregulation of Th1-type of immune response on Semliki Forest A7 virus infection in experimental autoimmune encephalomyelitis (**EAE**) susceptible Th1-prone SJL mice and in **EAE**-resistant Th2-prone BALB/c mice. We aimed at addressing the target-cell population of Linomide responsible for this Th1 downregulation. Treatment with Linomide led to increased virus infection in brain and this effect coincided with decreased production of IL-12 and IFN-gamma from stimulated spleen cells in SJL mice. In contrast, IL-12 and IFN-gamma expression were increased in Linomide-treated BALB/c mice. Treatment of infected SJL mice resulted in decreased percentage of CD11b+ and CD11c+ cells. Thus, the target cell population of Linomide may be antigen-presenting cells (APC) which are considered as candidates for regulatory cells of Th1/Th2 balance.

L46 ANSWER 2 OF 22 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2001:262556 Document No.: PREV200100262556. PPARgamma agonists prevent **EAE** by inhibiting IL-12 signaling through JAK-STAT pathway in T cells. Bright, John J. (1); Natarajan, Chandramohan (1); Large, Edward (1). (1) Vanderbilt University Medical Center, 2201 Capers Ave, 1222VSRH, Nashville, TN, 37212 USA. FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A1039. print. Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001 ISSN: 0892-6638. Language: English. Summary Language: English.
AB Peroxisome proliferator-activated receptor gamma (PPARgamma) is a nuclear receptor that regulates cell growth, differentiation and homeostasis. PPARgamma agonists are potent therapeutic agents for the treatment of diabetes, cancer and inflammatory diseases. IL-12 is a 70 kD heterodimeric cytokine produced mainly by macrophage, microglia and dendritic cells that play a critical role in the induction of T cell proliferation, IFNgamma production and Th1 differentiation. We and others have shown earlier that IL-12 plays a critical role in the pathogenesis of experimental allergic encephalomyelitis (**EAE**), a CD4+ Th1 cell-mediated inflammatory demyelinating **autoimmune disease model** of multiple sclerosis (MS). In this study we have examined the effects of PPARgamma agonists on IL-12 signaling, Th1 differentiation and the pathogenesis of **EAE**. Immunoprecipitation and Western blot analyses showed that 15-deoxy-delta-prostaglandin J2 (15d-PGJ2), a high affinity natural ligand for PPARgamma and Ciglitazone, a synthetic ligand for PPARgamma inhibit IL-12-induced tyrosine phosphorylation and activation of JAK2 and TYK2 kinases in activated T cells. The PPARgamma agonists also inhibited the tyrosine phosphorylation of STAT3 and STAT4 in T cells. The inhibition of JAK-STAT pathway by PPARgamma agonists resulted in the blockade of IL-12-induced T cell proliferation, IFNgamma production and Th1 differentiation. In vivo treatment (i.p., three doses per week) of SJL/J mice with 15d-PGJ2 (25 mg/dose) or Ciglitazone (100 mg/dose) following induction of **EAE** by active immunization with mouse spinal cord homogenate or adoptive transfer of myelin basis protein sensitized T cells significantly reduced the incidence and severity of **EAE**. These results suggested that PPARgamma agonists prevent **EAE** by inhibiting IL-12 signaling and IL-12 mediated Th1 differentiation in vivo. Further studies will define the potential use of PPARgamma agonists for the treatment of MS and other inflammatory disease of the brain.

L46 ANSWER 3 OF 22 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2002:157503 Document No.: PREV200200157503. Tolerance induction via gene therapy: Mechanisms and implications for autoimmunity and hemophiliac inhibitors. Scott, David W. (1); El-Amine, Moustapha (1); Litzinger, Mary (1); Melo, Marco E. F. (1); Qian, Jiahua (1). (1) Dept. of Immunology, Holland Lab of the American Red Cross, Rockville, MD USA. Blood, (November

16, 2001) Vol. 98, No. 11 Part 2, pp. 411b. http://www.bloodjournal.org/. print. Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 2 Orlando, Florida, USA December 07-11, 2001 ISSN: 0006-4971. Language: English.

AB A platform technology, in which we engineered retroviral constructs to drive expression of different antigens in frame at the N-terminus of a murine IgG1 heavy chain, has been utilized to design vectors for gene therapy of a number of autoimmune diseases and for inhibitor formation in hemophiliacs. We have shown that recipients of B-cell blasts transduced with these constructs are tolerant to the protein epitopes of the expressed genes. Thus, this gene therapy model allows us to induce tolerance to multiple antigenic determinants expressed in frame on a soluble IgG fusion protein scaffold. Tolerance was originally induced to model peptides, the phage lambda repressor cI sequence p1-102 or its immunodominant epitope (p12-26). Effective suppression of immunity can be achieved when LPS-activated B-cell blasts are transduced with fusion IgGs containing these epitopes and injected into naive or even primed recipients. Our results also suggest direct involvement of B cells and MHC presentation in tolerance. Recent data directly demonstrate that (transduced) LPS blasts divide and persist in the recipient's spleens for greater than 30 days, and that expression of FasL may be involved in the tolerance mechanism. Further studies in **autoimmune disease models** showed clinical efficacy in uveitis (J. Clin. Invest., 106:245, 2000). We have now extended this and will present data demonstrating amelioration of symptoms in multiple sclerosis/ **EAE** (with MBP-IgG), and diabetes (with insulin-IgG and GAD-IgG fusion proteins). Our data suggest that the donor B-cell APC (e.g., of the patient) choose the appropriate epitope for their MHC to present for tolerance. Efforts are underway with FVIII domains expressed with the IgG to extend this to inhibitor formation in hemophilia.

L46 ANSWER 4 OF 22 MEDLINE DUPLICATE 2

2001391367 Document Number: 21339012. PubMed ID: 11445281. Pertussis toxin-induced hyperacute autoimmune encephalomyelitis in Lewis rats is correlated with increased expression of inducible nitric oxide synthase and tumor necrosis factor alpha. Ahn M; Kang J; Lee Y; Riu K; Kim Y; Jee Y; Matsumoto Y; Shin T. (Department of Veterinary Medicine, Institute for Life Science, Brain Korea 21, SHRC, Cheju National University, 690-756, Jeju, South Korea.) NEUROSCIENCE LETTERS, (2001 Jul 27) 308 (1) 41-4. Journal code: 7600130. ISSN: 0304-3940. Pub. country: Ireland. Language: English.

AB The involvement of inducible nitric oxide synthase (iNOS) and tumor necrosis factor alpha (TNF-alpha), which have diverse roles in the progression of **autoimmune disease models**, was studied in pertussis toxin (PT)-induced hyperacute experimental autoimmune encephalomyelitis (**EAE**) in Lewis rats. The expression of TNF-alpha mRNA (increased 5-fold, $P<0.01$) and iNOS protein (3-fold, $P<0.01$) was much greater in the spinal cords with PT(+) **EAE** at the peak stage of **EAE** than in those with PT(-) **EAE**, as shown by competitive PCR and Western blot analysis, respectively. Immunohistochemistry showed that the majority of ED1-positive macrophages in **EAE** lesions contained iNOS, and that there were many more iNOS-positive cells in the CNS lesions of PT(+) rats than in those of PT(-) rats. These findings suggest that PT-induced hyperacute **EAE** is partly mediated by the enhanced expression of iNOS and TNF-alpha in the early stages of rat **EAE**.

L46 ANSWER 5 OF 22 MEDLINE DUPLICATE 3

2000235409 Document Number: 20235409. PubMed ID: 10772655. Role of passive T-cell death in chronic experimental autoimmune encephalomyelitis. Issazadeh S; Abdallah K; Chitnis T; Chandraker A; Wells A D; Turka L A; Sayegh M H; Khoury S J. (Center for Neurologic Diseases, Boston, Massachusetts 02115, USA.) JOURNAL OF CLINICAL INVESTIGATION, (2000 Apr)

105 (8) 1109-16. Journal code: 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB The mechanisms of chronic disease and recovery from relapses in experimental autoimmune encephalomyelitis (**EAE**), an animal model of multiple sclerosis, are unknown. Deletion of myelin-specific lymphocytes by apoptosis may play a role in termination of the inflammatory response. One pathway of apoptosis is the passive cell death or "cell death by neglect" pathway, which is under the control of the Bcl family of genes. To investigate the role of passive cell death pathway in **EAE**, we used mice with transgenic expression of the long form of the bcl-x gene (Bcl-x(L)) targeted to the T-cell lineage. We found that mice transgenic for Bcl-x(L) have an earlier onset and a more chronic form of **EAE** induced by myelin oligodendrocyte glycoprotein (MOG) peptide 35-55 compared with wild-type littermate mice. This was not due to an expanded autoreactive cell repertoire. Primed peripheral lymphocytes from Bcl-x(L) transgenic mice showed increased proliferation and cytokine production to MOG peptide in vitro compared with lymphocytes from wild-type animals. Immunohistologic studies demonstrated increased cellular infiltrates, immunoglobulin precipitation, and demyelination in the Bcl-x(L) transgenic central nervous system (CNS) compared with controls. There was also a decreased number of apoptotic cells in the CNS of Bcl-x(L) transgenic mice when compared with littermates at all time points tested. This is the first report of an **autoimmune disease model** in Bcl-x(L) transgenic mice. Our data indicate that the passive cell death pathway is important in the pathogenesis of chronic **EAE**. These findings have implications for understanding the pathogenesis of multiple sclerosis and other autoimmune diseases.

L46 ANSWER 6 OF 22 CAPLUS COPYRIGHT 2003 ACS

2000:243516 Document No. 132:249664 NKT cells in **autoimmune disease models**. Yamamura, Takashi (Div. Immunol., Natl. Inst. Neurosci., NCNP, Japan). Saishin Igaku, 55(4), 858-863 (Japanese) 2000. CODEN: SAIGAK. ISSN: 0370-8241. Publisher: Saishin Igakusha.

AB A review with 19 refs. on roles of NKT (natural killer T) cells in exptl. autoimmune encephalomyelitis (**EAE**). NKT cells suppress early pathogenesis of **EAE**, but excessive prodn. of IFN.gamma. (interferon .gamma.) from the NKT cells makes symptoms of **EAE** worse.

L46 ANSWER 7 OF 22 MEDLINE DUPLICATE 4

1998349357 Document Number: 98349357. PubMed ID: 9686568. Kinetics of expression of costimulatory molecules and their ligands in murine relapsing experimental autoimmune encephalomyelitis in vivo. Issazadeh S; Navikas V; Schaub M; Sayegh M; Khoury S. (Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA.) JOURNAL OF IMMUNOLOGY, (1998 Aug 1) 161 (3) 1104-12. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB We studied the kinetics of expression of costimulatory molecules and cytokines in the central nervous system (CNS) in murine relapsing experimental autoimmune encephalomyelitis (**EAE**). During the natural course of **EAE**, B7-2 expression in the CNS correlated with clinical signs, while B7-1 was exclusively expressed during remissions. Interestingly, B7-1 was expressed on infiltrating mononuclear cells as well as neuronal cells in the CNS. In the periphery, B7-1 expression on APCs peaked with clinical disease but decreased on T cells. CD28 and CTLA4 molecules, the two known ligands for B7-1 and B7-2, had distinct expression patterns in the CNS; CD28 was highly expressed and correlated with B7-2 expression on APCs (macrophages/microglia as well as astrocytes) and with the clinical signs of **EAE**. CTLA4, on the other hand, was expressed by substantially fewer cells during the effector phase of disease and peaked during remission, which is consistent with the emerging role of this molecule in the termination of immune responses. The

expression of CD40 and CD40L in the CNS was increased during clinical attacks. The expression of IL-12, IFN-gamma, and TNF-alpha correlated with disease activity and severity, while TGF-beta was the only factor that was up-regulated during the recovery phase. Interestingly, TGF-beta was also expressed by neurons during remission. This is the first study demonstrating the kinetics of the in vivo expression of costimulatory molecules, their ligands, and cytokines in an **autoimmune disease model** characterized by remissions and relapses. Our data suggest that the targeting of costimulatory molecules to block an immune response must take into account the expression patterns in the target organ.

L46 ANSWER 8 OF 22 MEDLINE
97344533 Document Number: 97344533. PubMed ID: 9200943. Immune intervention by peptides having a MHC class II binding motif--application of MHC blockers to **autoimmune disease models** . Nihira S. (Dept. Screening, Nippon Roche Research Center.) NIPPON RINSHO. JAPANESE JOURNAL OF CLINICAL MEDICINE, (1997 Jun) 55 (6) 1525-30. Ref: 21. Journal code: 0420546. ISSN: 0047-1852. Pub. country: Japan. Language: Japanese.

AB Intervention of T cell activation and the treatment of **autoimmune disease models** by MHC class II binding peptides was reviewed in this article. Analog peptides derived from antigenic peptides were shown to inhibit T cell activation in vitro as well as in vivo either by T cell antagonism, T cell tolerance induction, or by MHC blockade. The induction of immune suppression by MHC blocker peptides was discussed in detail. Successful application of MHC blocker peptides in the treatment of experimental allergy encephalomyelitis (**EAE**), non-obese diabetic mice and collagen-induced arthritis models indicated that in vivo blocking of MHC class II molecules represents a promising approach for the prevention and possibly treatment of human autoimmune diseases. An approach in identifying non-peptidic MHC blockers was also described.

L46 ANSWER 9 OF 22 MEDLINE DUPLICATE 5
1998067039 Document Number: 98067039. PubMed ID: 9403335. Reduction of disease causative T-cells in experimental **autoimmune disease models** by a new antirheumatic drug, TAK-603. Ohta Y; Fukuda S; Makino H. (Pharmaceutical Research Laboratories, Takeda Chemical Industries, Ltd., Osaka, Japan.) IMMUNOPHARMACOLOGY, (1997 Oct) 37 (2-3) 167-74. Journal code: 7902474. ISSN: 0162-3109. Pub. country: Netherlands. Language: English.

AB We investigated the mode of action of a new quinoline derivative, TAK-603 (ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmeth yl) quinoline-3-carboxylate), in adjuvant arthritis (AA), a model of rheumatoid arthritis. AA rat splenocytes transferred the arthritis to normal syngeneic rats upon inoculation, but the cells from AA rats treated with TAK-603 (6.25 mg/kg/day) caused only mild arthritis with significantly less foot pad swelling and a lower arthritis score. An effect of TAK-603 in the induction phase of AA was suggested. TAK-603 had little effect on CD4+ and CD8+ T-cell populations in the AA rat splenocytes. We therefore estimated the frequency of T-cells which are reactive to the so-called disease causative antigen using a limiting dilution assay (LDA). The ratio of T-cells responsive to PPD, which increased in AA rat splenocytes with the severity of the arthritis, was reduced in AA rats treated with TAK-603. Furthermore, the ratio of MBP (myelin basic protein)-reactive T-cells, which were generated in experimental allergic encephalomyelitis (**EAE**) rats, were also reduced by TAK-603 administration. These data suggest that TAK-603 acts on the immune system and reduces the number of cells reactive to the relevant antigen.

L46 ANSWER 10 OF 22 MEDLINE DUPLICATE 6
1998056768 Document Number: 98056768. PubMed ID: 9394786. Synergism

between sirolimus and 1,25-dihydroxyvitamin D3 in vitro and in vivo. Branisteanu D D; Mathieu C; Bouillon R. (Laboratory for Experimental Medicine and Endocrinology (LEGENDO), U.Z. Gasthuisberg, Katholieke Universiteit Leuven, Belgium.) JOURNAL OF NEUROIMMUNOLOGY, (1997 Nov) 79 (2) 138-47. Journal code: 8109498. ISSN: 0165-5728. Pub. country: Netherlands. Language: English.

AB The active form of vitamin D, 1 alpha, 25-(OH)2D3, displays immunomodulatory effects in vitro and in vivo at pharmacological levels. We evaluated the dose-effect relationship of 1,25(OH)2D3 and sirolimus (rapamycin, RAP) in vitro, on the inhibition of PHA-stimulated PBMC proliferation, by using the median effect analysis. Pharmacological concentrations of 1,25(OH)2D3 (between 10(-9) and 3 x 10(-6) M) interacted synergistically with RAP (combination index value of 0.01 for 50% suppression of PBMC proliferation). In vivo, the effect of 1,25(OH)2D3 and RAP combinations on the evolution of experimental allergic encephalomyelitis in SJL mice was analyzed. 1,25(OH)2D3, given i.p., in monotherapy, at a dose of 2 micrograms/kg every two days, from day -3 until day +19 after disease induction, or RAP, injected daily at a dose of 0.3 mg/kg for the same period, decreased **EAE** incidence (paralysis in 70 and 55% of the animals, respectively, versus 98% in the placebo treated group, $p < 0.001$). The combination treatment using the two drugs in these subtherapeutical doses provided near-total clinical (8% paralysis, $p < 0.001$ compared to monotherapy with 1,25(OH)2D3 or RAP) and histological protection, comparable to that obtained with RAP in monotherapy at a threefold higher dose (1 mg/kg/d). When the two drugs were given using an alternate day administration schedule (RAP at 0.6 mg/kg and 1,25(OH)2D3 at 2 micrograms/kg, each given on alternate days from day -3 to 19), near total protection was again obtained (13% paralysis, $p < 0.001$ versus control). These in vitro and in vivo data support the existence of synergistic interactions between 1,25(OH)2D3 and RAP. Considering the narrow therapeutic windows of both RAP and vitamin D-related compounds in **autoimmune disease models**, combinations of these drugs could find clinical application in reducing their individual therapeutically efficient doses to non-toxic levels.

L46 ANSWER 11 OF 22 MEDLINE DUPLICATE 7

97079119 Document Number: 97079119. PubMed ID: 8920851. Inactivation of T cell receptor peptide-specific CD4 regulatory T cells induces chronic experimental autoimmune encephalomyelitis (**EAE**). Kumar V; Stellrecht K; Sercarz E. (Department of Microbiology and Molecular Genetics, University of California, Los Angeles 90095-1489.) JOURNAL OF EXPERIMENTAL MEDICINE, (1996 Nov 1) 184 (5) 1609-17. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB T cell receptor (TCR)-recognizing regulatory cells, induced after vaccination with self-reactive T cells or TCR peptides, have been shown to prevent autoimmunity. We have asked whether this regulation is involved in the maintenance of peripheral tolerance to myelin basic protein (MBP) in an **autoimmune disease model**, experimental autoimmune encephalomyelitis (**EAE**). Antigen-induced **EAE** in (SJL x B10.PL)F1 mice is transient in that most animals recover permanently from the disease. Most of the initial encephalitogenic T cells recognize MBP Ac1-9 and predominantly use the TCR V beta 8.2 gene segment. In mice recovering from MBP-induced **EAE**, regulatory CD4+ T cells (Treg) specific for a single immunodominant TCR peptide B5 (76-101) from framework region 3 of the V beta 8.2 chain, become primed. We have earlier shown that cloned B5-reactive Treg can specifically downregulate responses to Ac1-9 and also protect mice from **EAE**. These CD4 Treg clones predominantly use the TCR V beta 14 or V beta 3 gene segments. Here we have directly tested whether deletion/blocking of the Treg from the peripheral repertoire affects the spontaneous recovery from **EAE**. Treatment of F1 mice with appropriate V beta-specific monoclonal antibodies resulted in an increase in the severity and duration of the

disease; even relapses were seen in one-third to one-half of the Treg-deleted mice. Interestingly, chronic disease in treated mice appears to be due to the presence of Ac1-9-specific T cells. Thus, once self-tolerance to MBP is broken by immunization with the antigen in strong adjuvant, TCR peptide-specific CD4 Treg cells participate in reestablishing peripheral tolerance. Thus, a failure to generate Treg may be implicated in chronic autoimmune conditions.

L46 ANSWER 12 OF 22 CAPLUS COPYRIGHT 2003 ACS
1997:69149 Document No. 126:156103 Molecular basis of autoimmune disease. Yamamoto, Kazuhiko (Med. Inst. Bioregul., Kyushu Univ., Fukuoka, 812-81, Japan). Molecular Medicine (Tokyo), Extra Vol.(451), 42-48 (Japanese) 1996. CODEN: MOLMEL. ISSN: 0918-6557. Publisher: Nakayama Shoten.
AB A review, with 9 refs., on the heterogeneity in onset of autoimmune diseases, the mechanism of immunol. tolerance by anergy and ignorant in T cell immunity, and anergy and clonal deletion in B cell tolerance. Mechanisms to onset of autoimmune diseases are discussed: presentation of cryptic antigen to immune system, mol. mimicry to induce cross-reaction, and ectopic expression of major histocompatibility antigen complex (MHC) class II. Th1 and Th2 imbalance induced autoimmune diseases. Immunol. difference between systemic and organ-specific autoimmune diseases are described. Anomaly is depicted in **autoimmune disease model** mice; NOD mouse, exptl. autoimmune encephalomyelitis (**EAE**) mouse, NZB/NZW F1 mouse as a model of systemic lupus erythematosus (SLE), and MRL/lpr mouse as a model for SLE and chronic rheumatoid arthritis.

L46 ANSWER 13 OF 22 MEDLINE DUPLICATE 8
95394023 Document Number: 95394023. PubMed ID: 7545112. Spreading of the immune response to different myelin basic protein peptides in chronic experimental autoimmune encephalomyelitis in B10.RIII mice. Jansson L; Diener P; Engstrom A; Olsson T; Holmdahl R. (Department of Medical Inflammation Research, Lund University, Sweden.) EUROPEAN JOURNAL OF IMMUNOLOGY, (1995 Aug) 25 (8) 2195-200. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.
AB B10.RIII mice develop chronic and relapsing experimental autoimmune encephalomyelitis (**EAE**) after immunization with the myelin basic protein (MBP) peptide 89-101 (VHFFKNIVTPRTP). To investigate the basis for the chronicity of the disease, the subsequent development of an immune responses to other parts of the MBP protein were investigated. Onset of disease occurs 9-25 days after immunization with MBP89-101. T cell responses towards a series of MBP peptides were assessed in an enzyme-linked immunospot assay detecting single cells secreting IFN-gamma. There were responses not only to MBP89-101, but also towards peptides derived from sequences outside of MBP89-101. These peptides were of two kinds: those with sequences completely outside the 89-101 stretch of MBP; and those sharing a short sequence with MBP89-101 depending on alternative splicing of MBP mRNA. Immunization with these peptides also produced chronic **EAE** and a spreading of the immune response to other MBP peptides. Immunization with stepped peptides around the relevant region (MBP87-110) showed that peptides sharing a 6-amino-acid motif induced **EAE** after immunization. After MBP89-101 peptide immunization, T cells isolated from lymph nodes did not cross-react in vitro to the other peptides sharing this motif. We suggest that one mechanism for the development of relapses during the disease course is the recruitment of new T cells with specificity for MBP peptides not derived from the peptide used for immunization. This is the first time such a mechanism has been demonstrated in a chronic **autoimmune disease model**.

L46 ANSWER 14 OF 22 MEDLINE DUPLICATE 9
94351070 Document Number: 94351070. PubMed ID: 8071434. Estrogen induces

a potent suppression of experimental autoimmune encephalomyelitis and collagen-induced arthritis in mice. Jansson L; Olsson T; Holmdahl R. (Department of Medical and Physiological Chemistry, Uppsala University, Sweden.) JOURNAL OF NEUROIMMUNOLOGY, (1994 Sep) 53 (2) 203-7. Journal code: 8109498. ISSN: 0165-5728. Pub. country: Netherlands. Language: English.

AB We have earlier described a chronic relapsing experimental autoimmune encephalomyelitis (**EAE**) in B10.RIII mice induced with a peptide of myelin basic protein (MBP), mimicking the course of multiple sclerosis in man. We now show that estrogens ameliorate chronic **EAE**. Castration of female mice led to an earlier disease onset (day 9 +/- 2 postimmunization (p.i.) in castrated mice vs. day 16 +/- 4 p.i. in normal mice). Long-term treatment with high levels of 17 beta-estradiol (E2) given as Silastic implants led to a dramatically delayed onset of disease in both castrated and normal female mice (mean onset day was day 39 +/- 14 and day 50 +/- 3, respectively). Treatment of castrated females by injections of E2, at a concentration which induces the serum levels seen at late stage pregnancy, delayed the onset approximately 1 week (mean onset 21 +/- 8). In contrast, treatment with estriol (E3), which was also given at doses corresponding to those levels seen during pregnancy, delayed the disease onset for a longer time (mean onset day 31 +/- 5). Five times higher doses of E2, compared with those seen during pregnancy, were required to obtain similar effects as the low E3 dose. The same mouse strain (B10.RIII) is also susceptible to induction of collagen-induced arthritis (CIA). We show here that also CIA is suppressed by the same treatments with E2 and E3, suggesting that similar estrogen-mediated mechanisms may operate to suppress these T-cell-dependent **autoimmune disease models**.

L46 ANSWER 15 OF 22 MEDLINE DUPLICATE 10

92364354 Document Number: 92364354. PubMed ID: 1380045. The immunopathology of acute experimental allergic encephalomyelitis induced with myelin proteolipid protein. T cell receptors in inflammatory lesions. Sobel R A; Kuchroo V K. (Department of Pathology, Massachusetts General Hospital, Boston 02114.) JOURNAL OF IMMUNOLOGY, (1992 Aug 15) 149 (4) 1444-51. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB To determine whether there is predominance of T cells expressing a particular TCR V beta chain in the inflammatory lesions of an **autoimmune disease model**, TCR expression was analyzed in central nervous system (CNS) tissues of mice with experimental allergic encephalomyelitis (**EAE**). Acute **EAE** was induced in SJL/J mice either by sensitization with a synthetic peptide corresponding to myelin proteolipid protein residues 139-151 or by adoptive transfer of myelin proteolipid protein peptide 139-151-specific encephalitogenic T cell clones. Mice were killed when they showed clinical signs of **EAE** or by 40 days after sensitization or T cell transfer. Cryostat CNS and lymphoid tissue sections were immunostained with a panel of mAb to T cell markers and proportions of stained cells were counted in inflammatory foci. In mice with both actively induced and adoptively transferred **EAE**, infiltrates consisted of many CD3+, TCR alpha beta+, and CD4+ cells, fewer CD8+ cells, and small numbers of TCR gamma delta+ cells. Approximately 30% of CD45+ leukocytes in the inflammatory foci were T cells. Cells expressing TCR V beta 2, 3, 4, 6, 7 and 14 were detected in the infiltrates, whereas TCR V beta 8 and 11, which that are deleted in SJL mice, were absent. When **EAE** was induced by transfer of T cell clones that use either V beta 2, 6, 10, or 17, there was also a heterogeneous accumulation of T cells in the lesions. Similar proportions of TCR V beta+ and gamma delta+ cells were detected in **EAE** lesions and in the spleens of the mice. Thus, at the time that clinical signs are present in acute **EAE**, peripherally derived, heterogeneous TCR V beta+ cells are found in CNS lesions, even when the immune response is initiated to a short peptide Ag or by a T cell clone

using a single TCR V beta.

L46 ANSWER 16 OF 22 CAPLUS COPYRIGHT 2003 ACS
1992:488539 Document No. 117:88539 Spreading of T-cell autoimmunity to cryptic determinants of an autoantigen. Lehmann, Paul V.; Forsthuber, Thomas; Miller, Alexander; Sercarz, Eli E. (Dep. Microbiol. Mol. Genet., Univ. California, Los Angeles, CA, 90024, USA). Nature (London, United Kingdom), 358(6382), 155-7 (English) 1992. CODEN: NATUAS. ISSN: 0028-0836.
AB Immunization with myelin basic protein (MBP) induces exptl. allergic encephalomyelitis (**EAE**), a prototype of CD4+ T-cell mediated autoimmune disease. In rodents, MBP-reactive T-cell clones are specific for a single, dominant determinant on MBP and use a highly restricted no. of T-cell receptor genes. Accordingly, **EAE** has been prevented by various receptor-specific treatments, suggesting similar strategies may be useful for therapy of human autoimmune disease. Here, in (SJL .times. B10.PL)F1 mice, immune dominance of a single determinant, MBP:Ac1-11, is confined to the inductive phase of **EAE**. In mice with chronic **EAE**, several addnl. determinants of MBP in peptides 35-47, 81-100 and 121-140 recall proliferative responses. Most importantly, reactivity to the latter determinants was also detected after induction of **EAE** with MBP peptide Ac1-11 alone; this demonstrates priming by endogenous MBP determinants. Thus, determinants of MBP that are cryptic after primary immunization can become immunogenic in the course of **EAE**. Diversification of the autoreactive T-cell repertoire due to determinant spreading has major implications for the pathogenesis of, and the therapeutic approach to, T-cell driven autoimmune disease.

L46 ANSWER 17 OF 22 CAPLUS COPYRIGHT 2003 ACS
1992:462553 Document No. 117:62553 Effect of poriatin on the induction of experimental autoimmune encephalomyelitis in Wistar rats. Wang, Guojun; Li, Siying; Xu, Jin (Inst. Med. Biotechnol., Beijing, 100050, Peop. Rep. China). Zhongguo Kangshengsu Zazhi, 17(1), 38-41 (Chinese) 1992. CODEN: ZKZAEY. ISSN: 1001-8689.
AB Exptl. autoimmune encephalomyelitis (**EAE**) is an **autoimmune disease model** in lab. animals caused by cell-mediated injury. Using guinea-pig spinal cord homogenate in complete Freund adjuvant and Bordetella pertussis vaccine, **EAE** was successfully induced in Wistar rats. The induction rate was >95%. When treated with poriatin (50-200 mg/kg/d .times. 16d, p.o.) or cyclophosphamide (5 mg/kg/d .times. 16d, i.p.), the incidence of **EAE** was decreased. In addn., poriatin showed a synergistic effect on suppression of **EAE** by cyclophosphamide. The ED of cyclophosphamide was reduced by poriatin coadministration. These results suggest that poriatin may have potential use in the treatment of autoimmune diseases.

L46 ANSWER 18 OF 22 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 11
92140117 EMBASE Document No.: 1992140117. Immunosuppressive therapy with anti-rat T-cell receptor monoclonal antibody R73 in various experimental autoimmune diseases of the rat. Schorlemmer H.U.; Kanzy E.J.; Kurrle R.; Seiler F.R.. Research Department Immunology, Behringwerke AG, P.O. Box 11 40,D-3550 Marburg/Lahn, Germany. International Journal of Immunotherapy 7/4 (161-168) 1991.
ISSN: 0255-9625. CODEN: IJIMET. Pub. Country: Switzerland. Language: English. Summary Language: English.
AB Anti-rat .alpha./.beta.-T-cell receptor (TCR) monoclonal antibody (MAb) R73 was investigated as to its disease-modifying activity on adjuvant arthritis (AA), on experimental allergic encephalomyelitis (**EAE**) and on a local graft versus host (CvH) reaction (popliteal lymph nodes = PLN) in Lewis Brown-Norway rats. MAb R73 was able to prevent the onset of adjuvant disease provided therapy was started within the first 12 days after its induction. If therapy started after the establishment of AA,

this MAb was still able to reduce the degree of chronic inflammation and to arrest its progress. Intravenous application of MAb R73 also reduced the signs of **EAE** and prevented mortality. This was even seen when the MAb was given after the outbreak of clinical symptoms. In a model of local CvH reaction, MAb R73 also acted therapeutically and lowered the PLN weights, reflecting immunosuppressive activity. Even more importantly, F(ab)2 fragments of R73 significantly suppressed disease development in the above-mentioned **autoimmune disease models** . Analogy in model systems strongly suggests that the results of therapeutic MAb protocols in animal models can be directly transferred to protocols for clinical application.

L46 ANSWER 19 OF 22 MEDLINE DUPLICATE 12
92129218 Document Number: 92129218. PubMed ID: 1774194. Autoimmunity in non-human primates: the role of major histocompatibility complex and T cells, and implications for therapy. Jonker M; Bakker K; Slierendregt B; Hart B; Bontrop R. (Institute of Applied Radiobiology and Immunology TNO, Rijswijk, The Netherlands.) HUMAN IMMUNOLOGY, (1991 Sep) 32 (1) 31-40. Journal code: 8010936. ISSN: 0198-8859. Pub. country: United States. Language: English.

AB Two **autoimmune disease models** were studied in rhesus monkeys: type II collagen-induced arthritis (CIA) and experimental allergic encephalomyelitis (**EAE**). Unrelated outbred animals were used in these studies. In both models disease resistant and susceptible individuals could be identified. Susceptibility correlated with in vitro cellular responsiveness to antigen in the CIA model. In both models resistant as well as susceptible individuals developed a humoral response to the inducing antigen. However, there is an indication that IgM antibodies play a crucial role in the induction of CIA. No clear association between major histocompatibility complex (MHC) type and disease incidence was found although a higher frequency of a certain DR type was observed in **EAE** susceptible monkeys. It is likely that both the antigen binding capacity of the MHC class II molecules and the T-cell repertoire play an important role in determining whether disease will develop or not.

L46 ANSWER 20 OF 22 SCISEARCH COPYRIGHT 2003 ISI (R)
91:666597 The Genuine Article (R) Number: GR589. T-CELL VACCINATION DOES NOT INDUCE RESISTANCE TO EXPERIMENTAL AUTOIMMUNE NEURITIS. JUNG S (Reprint); SCHLUESENER H J; TOYKA K; HARTUNG H P. UNIV WURZBURG, DEPT NEUROL, NEUROIMMUNOL BRANCH, JOSEF SCHNEIDER STR 11, W-8700 WURZBURG, GERMANY (Reprint); UNIV WURZBURG, MS CLIN RES GRP, W-8700 WURZBURG, GERMANY. JOURNAL OF NEUROIMMUNOLOGY (1991) Vol. 35, No. 1-3, pp. 1-11. Pub. country: GERMANY. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The effectiveness of T cell vaccination was analyzed in experimental autoimmune neuritis (EAN) that can be induced by immunization with bovine P2 protein or a peptide representing the amino acids 53-78 of P2 (P2 53-78). Lewis rats were vaccinated with glutaraldehyde-fixed lymph node cells which had been primed in vivo with P2 protein or P2 53-78 and had been activated in vitro with concanavalin A. Vaccinated animals were not protected from EAN induced by immunization with P2 protein in complete Freund's adjuvant (CFA). In a second set of experiments Lewis rats were vaccinated with irradiated or fixed P2-specific T cell lines of different specificity and neuritogenicity and were subsequently challenged with P2 53-78 in CFA. Likewise, severity of P2 53-78-induced EAN was not different between naive and T line-vaccinated groups. In spleens of vaccinated animals a substantial suppressive activity was demonstrated which was positively correlated with a weak anti-ergotypic response of these spleen cells. The fact that development of actively induced EAN was not prevented or even mitigated by T cell vaccination, in spite of an apparent vaccination-induced response to and on T lymphocytes, suggests that protection from disease is not readily induced in every **autoimmune**

disease model.

L46 ANSWER 21 OF 22 MEDLINE DUPLICATE 13
87168532 Document Number: 87168532. PubMed ID: 3549982. The immunopathology of acute experimental allergic encephalomyelitis. IV. An ultrastructural immunocytochemical study of class II major histocompatibility complex molecule (Ia) expression. Sobel R A; Natale J M; Schneeberger E E. JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY, (1987 May) 46 (3) 239-49. Journal code: 2985192R. ISSN: 0022-3069. Pub. country: United States. Language: English.

AB Cell surface expression of Class II major histocompatibility complex (Ia) molecules is required for antigen recognition by T cells. To determine the ultrastructural cellular distribution of Ia molecules in the **autoimmune disease model** acute experimental allergic encephalomyelitis (**EAE**) we studied central nervous system (CNS) tissues from adult Strain 13 guinea pigs (GP). Experimental allergic encephalomyelitis was induced by sensitization with GP spinal cord homogenate in complete Freund's adjuvant (CFA). Nine of 11 sensitized GP had clinical and histologic **EAE** whereas unsensitized and CFA-sensitized controls were normal. Central nervous system tissues were reacted with monoclonal antibodies to either GP Ia or T cell surface antigen using an avidin-biotin immunoperoxidase technique and studied by electron microscopy; Ia was found on luminal but not abluminal surfaces of many meningeal and parenchymal vascular endothelial cells in GP with **EAE**. In **EAE** perivascular lymphocytes and macrophages and processes of unidentified cells in the parenchyma expressed surface Ia and Ia+ macrophages encircled and phagocytosed myelin. T cells were found predominantly in perivascular inflammatory cuffs. These observations indicate that following immunologic challenge Ia is expressed on luminal surfaces of vascular endothelium and on resident CNS cells, suggesting the possibility that these cells may have active antigen-presenting functions in CNS inflammatory reactions.

L46 ANSWER 22 OF 22 MEDLINE DUPLICATE 14
75134392 Document Number: 75134392. PubMed ID: 47366. Experimental autoimmune encephalomyelitis in mice: immunologic response to mouse spinal cord and myelin basic proteins. Bernard C C; Carnegie P R. JOURNAL OF IMMUNOLOGY, (1975 May) 114 (5) 1537-40. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB It was confirmed that experimental autoimmune encephalomyelitis **EAE**, could be induced in SJL/J mice with mouse spinal cord homogenate. It was shown that induction of **EAE** in mice was critically dependent on the concentration of pertussis vaccine. The encephalitogen present in mouse brain was the basic protein of myelin. The smaller form of the mouse and rat basic proteins induced **EAE**; thus the mouse like the rat responds to determinants other than the "tryptophan region," which induced **EAE** in guinea-pigs. Mice with **EAE** developed a cell-mediated immune response to myelin basic protein, as judged by inhibition of peritoneal cell migration. However, levels of antibody to mouse basic protein were low, as judged by radioimmunoassay. The establishment of this **autoimmune disease model** in the mouse will allow the application of well established techniques for the analysis of the immunologic mechanisms leading to disease manifestation.

=> d his

(FILE 'HOME' ENTERED AT 09:36:19 ON 11 MAR 2003)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 09:36:33 ON 11 MAR 2003
L1 0 S GLAT DERIVATIVE

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L2          748 S GLATIRAMER ACETATE
L3          257 S L2 AND COPOLYMER 1
L4            5 S L3 AND DERIVATIVE
L5            1 DUP REMOVE L4 (4 DUPLICATES REMOVED)
L6          515 S L2 AND TREATMENT
L7          128 S L6 AND AUTOIMMUNE
L8            0 S L7 AND T CELL MEDIATED
L9            3 S L7 AND RHEUMATOID ARTHRITIS
L10           3 DUP REMOVE L9 (0 DUPLICATES REMOVED)
L11          45 S L7 AND INFLAMMATORY
L12          20 DUP REMOVE L11 (25 DUPLICATES REMOVED)
L13           0 S L7 AND OSTEOARTHRITIS
L14         126 S L7 AND MULTIPLE SCLEROSIS
L15          62 DUP REMOVE L14 (64 DUPLICATES REMOVED)
L16           0 S L7 AND HEMOLYTIC ANEMIA
L17           0 S L7 AND OOPHORITIS
L18           0 S L7 AND THYROIDITIS
L19           0 S L7 AND UVEORETINITIS
L20           0 S L7 AND CROHN DISEASE
L21           0 S L7 AND "CROHN'S DISEASE"
L22           0 S L7 AND THROMOCYTOPENIC PURPURA
L23           0 S L7 AND COLITIS
L24           0 S L23 AND ALLERGY
L25           0 S L7 AND CONTACT SENSITIVITY
L26           0 S L7 AND DIABETES MELLITUS
L27           1 S L7 AND GRAVES DISEASE
L28           0 S L7 AND "GUILLAIN BARRE'S SYNDROME"
L29           0 S L7 AND "HASHIMOTO'S DISEASE"
L30           0 S L7 AND IDIOPATHIC MYXEDEMA
L31           0 S L7 AND MYASTHENIA GRAVIS
L32           1 S L7 AND PSORIASIS
L33           0 S L7 AND PEMPHIGUS VULGARIS
L34           0 S L7 AND SYSTEMIC LUPUS ERYTHEMATOSUS
L35           0 S L7 AND GVHD
L36           0 S L7 AND GRAFT VERSUS HOST DISEASE
L37           1 S L7 AND DELAYED TYPE HYPERSENSITIVITY
L38        1016 S (GAD A?/AU OR LIS D?/AU)
L39           0 S L38 AND GLATIRAMER ACETATE DERIVATIVE
L40           4 S L38 AND COPOLYMER 1
L41           3 DUP REMOVE L40 (1 DUPLICATE REMOVED)
L42           1 S L38 AND GLAT COPOLYMER
L43           0 S L38 AND TV MARKER
L44         449 S AUTOIMMUNE DISEASE MODEL
L45          71 S L44 AND EAE
L46          22 DUP REMOVE L45 (49 DUPLICATES REMOVED)

=> s l44 and multiple sclerosis
L47          38 L44 AND MULTIPLE SCLEROSIS

=> dup remove l47
PROCESSING COMPLETED FOR L47
L48          24 DUP REMOVE L47 (14 DUPLICATES REMOVED)

=> d l48 1-24 cbib abs

L48  ANSWER 1 OF 24  SCISEARCH  COPYRIGHT 2003 ISI (R)
2002:968093   The Genuine Article (R) Number: 619LX. Antigen-based
     immunotherapy drives the prcocious development of autoimmunity.  Tian J;
     Olcott A P; Kaufman D L (Reprint). Univ Calif Los Angeles, Dept Mol & Med
     Pharmacol, Sch Med, Los Angeles, CA 90095 USA (Reprint). JOURNAL OF
     IMMUNOLOGY (1 DEC 2002) Vol. 169, No. 11, pp. 6564-6569. Publisher: AMER
     ASSOC IMMUNOLOGISTS. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA. ISSN:
     0022-1767. Pub. country: USA. Language: English.
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ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB During the development of type I diabetes mellitus in nonobese diabetic (NOD) mice, T cell autoimmunity gradually spreads among beta cell Ags. Little is known about how autoantigen-based immunotherapies affect this spreading hierarchy. We treated newborn NOD mice with different autoantigenic beta cell peptides (in adjuvant) and characterized their T cell responses at 4 wk of age, when autoimmunity is usually just beginning to arise to a few beta cell Ag determinants. Surprisingly, we found that regardless of whether an early, or late target determinant was administered, autoimmunity had already arisen to all tested beta cell autoantigen determinants, far in advance of when autoimmunity would have naturally arisen to these determinants. Thus, rather than limiting the loss of self-tolerance, immunotherapy caused the natural spreading hierarchy to be bypassed and autoreactivities to develop precociously. Evidently, young NOD mice have a broad array of beta cell-reactive T cells whose activation/expansion can occur rapidly after treatment with a single beta cell autoantigen. Notably, the precocious autoreactivities were Th2 type, with the exception that a burst of precocious Th1 responses was also induced to the injected autoantigen and there were always some Th1 responses to glutamic acid decarboxylase. Similarly treated type 1 diabetes mellitus-resistant mouse strains developed Th2 responses only to the injected Ag. Thus, autoantigen administration can induce a cascade of autoimmune responses in healthy (preautoimmune) mice that are merely genetically susceptible to spontaneous autoimmune disease. Such phenomena have not been observed in experimental **autoimmune disease models** and may have important clinical implications.

L48 ANSWER 2 OF 24 MEDLINE DUPLICATE 1

2002620788 Document Number: 22265641. PubMed ID: 12377928. Experimental basis of hematopoietic stem cell transplantation for treatment of autoimmune diseases. van Bekkum D W. (Crucell B.V., Leiden, The Netherlands.) JOURNAL OF LEUKOCYTE BIOLOGY, (2002 Oct) 72 (4) 609-20. Ref: 94. Journal code: 8405628. ISSN: 0741-5400. Pub. country: United States. Language: English.

AB Experiments with animal models of autoimmune disease provided the rational and stimulus for the current, clinical studies of autologous stem cell transplantation for the treatment of a variety of severe, refractory, autoimmune diseases. The discoveries that led to the recognition of the key role of hematopoietic stem cells and the successful treatment of autoimmune diseases with bone marrow transplants are reviewed. The relevance of spontaneous and induced **autoimmune disease models** for the development of clinical treatment regimens is discussed. Most of the investigations with autologous stem cell transplantation have been performed with induced autoimmune disorders: in rats with adjuvant arthritis and in rats or mice with experimental, allergic encephalomyelitis, the current model for **multiple sclerosis**. The main aspects of this translational research were the conditioning regimens and the degree of T cell depletion of the graft as determinants of remission induction and the incidence of relapses. The emerging recommendations are compared with the outcome so far of the clinical studies.

L48 ANSWER 3 OF 24 SCISEARCH COPYRIGHT 2003 ISI (R)

2002:986505 The Genuine Article (R) Number: 620PU. Semliki Forest virus infection is enhanced in Th1-prone SJL mice but not in Th2-prone BALB/c mice during linomide-induced immunomodulation. Peltoniemi J (Reprint); Setala N; Broberg E; Roytta M; Hukkanen V; Salmi A A; Eralinna J P. Univ Turku, Dept Virol, Kiinamyllynkatu 13, FIN-20520 Turku, Finland (Reprint); Univ Turku, Dept Virol, FIN-20520 Turku, Finland; Univ Turku, Turku Immunol Ctr, MediCity Res Ctr, FIN-20520 Turku, Finland; Turku Grad Sch Biomed Sci, Turku, Finland; Univ Turku, Dept Pathol, FIN-20520 Turku, Finland; Univ Turku, Cent Hosp, Dept Neurol, FIN-20520 Turku, Finland.

JOURNAL OF NEUROIMMUNOLOGY (NOV 2002) Vol. 132, No. 1-2, pp. 83-92. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS . ISSN: 0165-5728. Pub. country: Finland. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Linomide (quinoline-3-carboxamide) is an immunomodulator with diverse effects on the immune system. Its beneficial effects on experimental **autoimmune disease models** have been linked to downregulation of Th1 cytokines and altered macrophage functions. We studied this effect of downregulation of Th1-type of immune response on Semliki Forest A7 virus infection in experimental autoimmune encephalomyelitis (EAE) susceptible Th1-prone SJL mice and in EAE-resistant Th2-prone BALB/c mice. We aimed at addressing the target-cell population of Linomide responsible for this Th1 downregulation. Treatment with Linomide led to increased virus infection in brain and this effect coincided with decreased production of IL-12 and IFN-gamma from stimulated spleen cells in SJL mice. In contrast, IL-12 and IFN-gamma expression were increased in Linomide-treated BALB/c mice. Treatment of infected SJL mice resulted in decreased percentage of CD11b+ and CD11c+ cells. Thus, the target cell population of Linomide may be antigen-presenting cells (APC) which are considered as candidates for regulatory cells of Th1/Th2 balance.

L48 ANSWER 4 OF 24 CAPLUS COPYRIGHT 2003 ACS

2001:850859 Document No. 135:370655 Models of chronic and acute inflammatory diseases. Ehrhardt, Rolf; Hong, Kenneth (Bioseek, Inc., USA). PCT Int. Appl. WO 2001087057 A1 20011122, 40 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US15215 20010510. PRIORITY: US 2000-PV203982 20000512.

AB The authors disclose the generation and manipulation of non-human animal models of T-cell-based inflammation. In the models, immunocompromised host animals are injected with a population of immunocompetent effector cells, depleted of CD25+ T cells. The effector cells are tolerant of the host major histocompatibility antigens, but reactive to at least one antigen present in the host animal. The transferred cells are preferably stimulated and localized by administration of an immunostimulant at a local site. In one example, C.B17/scid mice received CD25- mononuclear cells from Balb/c donors in conjunction with lipopolysaccharide as a model of psoriasis. Administration of anti-interleukin-12 monoclonal antibody ameliorated disease pathogenesis while co-administration of an adenovirus vector expressing a model antigen aggravated the disease pathol.

L48 ANSWER 5 OF 24 CAPLUS COPYRIGHT 2003 ACS

2001:760326 Document No. 135:317482 Pyruvate carboxylase-targeted diagnostics and therapeutics for autoimmune diseases. Ikushima, Hideto; Kojima, Shinichi; Sakai, Osamu (Sumitomo Pharmaceuticals Co., Ltd., Japan). Jpn. Kokai Tokkyo Koho JP 2001289855 A2 20011019, 14 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 2000-107690 20000410.

AB Provided are autoimmune disease diagnostic and therapeutic agents that target pyruvate carboxylase. The diagnostic and therapeutic agents detect or regulate the expression of pyruvate carboxylase gene. Anti-pyruvate carboxylase antibody, streptavidin, avidin, anti-biotin antibody, and their labeled analogs; as well as oligonucleotide probes and primers for hybridization and PCR, are useful as diagnostic agent. Non-human **autoimmune disease model** animals and plasmids comprising reporter gene-linked expression regulatory sequence of pyruvate

carboxylase gene are used for study of autoimmune diseases and for screening therapeutics and preventives. Adenovirus vector encoding pyruvate carboxylase gene may be used for gene therapy. The autoimmune diseases include chronic rheumatoid arthritis, systemic lupus erythematosus, and/or **multiple sclerosis**.

L48 ANSWER 6 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2001:262556 Document No.: PREV200100262556. PPARgamma agonists prevent EAE by inhibiting IL-12 signaling through JAK-STAT pathway in T cells. Bright, John J. (1); Natarajan, Chandramohan (1); Large, Edward (1). (1) Vanderbilt University Medical Center, 2201 Capers Ave, 1222VSRH, Nashville, TN, 37212 USA. FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A1039. print. Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001 ISSN: 0892-6638. Language: English. Summary Language: English.
AB Peroxisome proliferator-activated receptor gamma (PPARgamma) is a nuclear receptor that regulates cell growth, differentiation and homeostasis. PPARgamma agonists are potent therapeutic agents for the treatment of diabetes, cancer and inflammatory diseases. IL-12 is a 70 kD heterodimeric cytokine produced mainly by macrophage, microglia and dendritic cells that play a critical role in the induction of T cell proliferation, IFNgamma production and Th1 differentiation. We and others have shown earlier that IL-12 plays a critical role in the pathogenesis of experimental allergic encephalomyelitis (EAE), a CD4+ Th1 cell-mediated inflammatory demyelinating **autoimmune disease model** of **multiple sclerosis** (MS). In this study we have examined the effects of PPARgamma agonists on IL-12 signaling, Th1 differentiation and the pathogenesis of EAE. Immunoprecipitation and Western blot analyses showed that 15-deoxy-delta-prostaglandin J2 (15d-PGJ2), a high affinity natural ligand for PPARgamma and Ciglitazone, a synthetic ligand for PPARgamma inhibit IL-12-induced tyrosine phosphorylation and activation of JAK2 and TYK2 kinases in activated T cells. The PPARgamma agonists also inhibited the tyrosine phosphorylation of STAT3 and STAT4 in T cells. The inhibition of JAK-STAT pathway by PPARgamma agonists resulted in the blockade of IL-12-induced T cell proliferation, IFNgamma production and Th1 differentiation. In vivo treatment (i.p., three doses per week) of SJL/J mice with 15d-PGJ2 (25 mg/dose) or Ciglitazone (100 mg/dose) following induction of EAE by active immunization with mouse spinal cord homogenate or adoptive transfer of myelin basis protein sensitized T cells significantly reduced the incidence and severity of EAE. These results suggested that PPARgamma agonists prevent EAE by inhibiting IL-12 signaling and IL-12 mediated Th1 differentiation in vivo. Further studies will define the potential use of PPARgamma agonists for the treatment of MS and other inflammatory disease of the brain.

L48 ANSWER 7 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2002:157503 Document No.: PREV200200157503. Tolerance induction via gene therapy: Mechanisms and implications for autoimmunity and hemophiliac inhibitors. Scott, David W. (1); El-Amine, Moustapha (1); Litzinger, Mary (1); Melo, Marco E. F. (1); Qian, Jiahua (1). (1) Dept. of Immunology, Holland Lab of the American Red Cross, Rockville, MD USA. Blood, (November 16, 2001) Vol. 98, No. 11 Part 2, pp. 411b. http://www.bloodjournal.org/. print. Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 2 Orlando, Florida, USA December 07-11, 2001 ISSN: 0006-4971. Language: English.
AB A platform technology, in which we engineered retroviral constructs to drive expression of different antigens in frame at the N-terminus of a murine IgG1 heavy chain, has been utilized to design vectors for gene therapy of a number of autoimmune diseases and for inhibitor formation in hemophiliacs. We have shown that recipients of B-cell blasts transduced with these constructs are tolerant to the protein epitopes of the expressed genes. Thus, this gene therapy model allows us to induce

tolerance to multiple antigenic determinants expressed in frame on a soluble IgG fusion protein scaffold. Tolerance was originally induced to model peptides, the phage lambda repressor cI sequence p1-102 or its immunodominant epitope (p12-26). Effective suppression of immunity can be achieved when LPS-activated B-cell blasts are transduced with fusion IgGs containing these epitopes and injected into naive or even primed recipients. Our results also suggest direct involvement of B cells and MHC presentation in tolerance. Recent data directly demonstrate that (transduced) LPS blasts divide and persist in the recipient's spleens for greater than 30 days, and that expression of FasL may be involved in the tolerance mechanism. Further studies in **autoimmune disease models** showed clinical efficacy in uveitis (J. Clin. Invest., 106:245, 2000). We have now extended this and will present data demonstrating amelioration of symptoms in **multiple sclerosis**/EAE (with MBP-IgG), and diabetes (with insulin-IgG and GAD-IgG fusion proteins). Our data suggest that the donor B-cell APC (e.g., of the patient) choose the appropriate epitope for their MHC to present for tolerance. Efforts are underway with FVIII domains expressed with the IgG to extend this to inhibitor formation in hemophilia.

L48 ANSWER 8 OF 24 SCISEARCH COPYRIGHT 2003 ISI (R)

2001:643588 The Genuine Article (R) Number: 460JQ. Circulating V alpha 24(+) V beta 11(+) NKT cell numbers are decreased in a wide variety of diseases that are characterized by autoreactive tissue damage. van der Vliet H J J (Reprint); von Blomberg B M E; Nishi N; Reijm M; Voskuyl A E; van Bodegraven A A; Polman C H; Rustemeyer T; Lips P; van den Eertwegh A J M; Giaccone G; Scheper R J; Pinedo H M. Free Univ Amsterdam Hosp, Dept Med Oncol, De Boelelaan 1117, NL-1081 HV Amsterdam, Netherlands (Reprint); Free Univ Amsterdam Hosp, Dept Med Oncol, NL-1081 HV Amsterdam, Netherlands; Free Univ Amsterdam Hosp, Dept Pathol, NL-1081 HV Amsterdam, Netherlands; Free Univ Amsterdam Hosp, Dept Rheumatol, NL-1081 HV Amsterdam, Netherlands; Free Univ Amsterdam Hosp, Dept Gastroenterol, NL-1081 HV Amsterdam, Netherlands; Free Univ Amsterdam Hosp, Dept Neurol, NL-1081 HV Amsterdam, Netherlands; Free Univ Amsterdam Hosp, Dept Dermatol, NL-1081 HV Amsterdam, Netherlands; Free Univ Amsterdam Hosp, Dept Epidemiol, NL-1081 HV Amsterdam, Netherlands. CLINICAL IMMUNOLOGY (AUG 2001) Vol. 100, No. 2, pp. 144-148. Publisher: ACADEMIC PRESS INC. 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA. ISSN: 1521-6616. Pub. country: Netherlands. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Natural killer T (NKT) cells have been implicated as playing an important role in regulating immune responses. Defects in the NRT cell population were reported in animal **autoimmune disease models** and in distinct human autoimmune diseases. Here, we report that circulating V alpha 24(+) V beta 11(+) NKT cell numbers are decreased in a broad variety of disorders with (auto)immune-mediated pathology, affecting the skin, bowel, central nervous system, and joints, regardless of disease duration or activity. Remarkably, normal circulating V alpha 24(+) V beta 11(+) NKT cell numbers were found in Graves disease and coeliac disease. Since earlier studies noted a rise in NRT cells in myasthenia gravis, the picture emerges in which a defective NKT cell population is associated with autoreactive tissue damage rather than with the propensity to develop autoimmune disease. The present data support the idea that therapies aiming at the in vivo expansion of regulatory NKT cells might help to control immune-mediated damage in autoimmune disease. (C) 2001 Academic Press.

L48 ANSWER 9 OF 24 MEDLINE

2001391367 Document Number: 21339012. PubMed ID: 11445281. Pertussis toxin-induced hyperacute autoimmune encephalomyelitis in Lewis rats is correlated with increased expression of inducible nitric oxide synthase and tumor necrosis factor alpha. Ahn M; Kang J; Lee Y; Riu K; Kim Y; Jee Y; Matsumoto Y; Shin T. (Department of Veterinary Medicine, Institute for

Life Science, Brain Korea 21, SHRC, Cheju National University, 690-756, Jeju, South Korea.) NEUROSCIENCE LETTERS, (2001 Jul 27) 308 (1) 41-4. Journal code: 7600130. ISSN: 0304-3940. Pub. country: Ireland. Language: English.

AB The involvement of inducible nitric oxide synthase (iNOS) and tumor necrosis factor alpha (TNF-alpha), which have diverse roles in the progression of **autoimmune disease models,** was studied in pertussis toxin (PT)-induced hyperacute experimental autoimmune encephalomyelitis (EAE) in Lewis rats. The expression of TNF-alpha mRNA (increased 5-fold, P<0.01) and iNOS protein (3-fold, P<0.01) was much greater in the spinal cords with PT(+) EAE at the peak stage of EAE than in those with PT(-) EAE, as shown by competitive PCR and Western blot analysis, respectively. Immunohistochemistry showed that the majority of ED1-positive macrophages in EAE lesions contained iNOS, and that there were many more iNOS-positive cells in the CNS lesions of PT(+) rats than in those of PT(-) rats. These findings suggest that PT-induced hyperacute EAE is partly mediated by the enhanced expression of iNOS and TNF-alpha in the early stages of rat EAE.

L48 ANSWER 10 OF 24 MEDLINE DUPLICATE 2

2000235409 Document Number: 20235409. PubMed ID: 10772655. Role of passive T-cell death in chronic experimental autoimmune encephalomyelitis. Issazadeh S; Abdallah K; Chitnis T; Chandraker A; Wells A D; Turka L A; Sayegh M H; Khoury S J. (Center for Neurologic Diseases, Boston, Massachusetts 02115, USA.) JOURNAL OF CLINICAL INVESTIGATION, (2000 Apr) 105 (8) 1109-16. Journal code: 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB The mechanisms of chronic disease and recovery from relapses in experimental autoimmune encephalomyelitis (EAE), an animal model of **multiple sclerosis,** are unknown. Deletion of myelin-specific lymphocytes by apoptosis may play a role in termination of the inflammatory response. One pathway of apoptosis is the passive cell death or "cell death by neglect" pathway, which is under the control of the Bcl family of genes. To investigate the role of passive cell death pathway in EAE, we used mice with transgenic expression of the long form of the bcl-x gene (Bcl-x(L)) targeted to the T-cell lineage. We found that mice transgenic for Bcl-x(L) have an earlier onset and a more chronic form of EAE induced by myelin oligodendrocyte glycoprotein (MOG) peptide 35-55 compared with wild-type littermate mice. This was not due to an expanded autoreactive cell repertoire. Primed peripheral lymphocytes from Bcl-x(L) transgenic mice showed increased proliferation and cytokine production to MOG peptide in vitro compared with lymphocytes from wild-type animals. Immunohistologic studies demonstrated increased cellular infiltrates, immunoglobulin precipitation, and demyelination in the Bcl-x(L) transgenic central nervous system (CNS) compared with controls. There was also a decreased number of apoptotic cells in the CNS of Bcl-x(L) transgenic mice when compared with littermates at all time points tested. This is the first report of an **autoimmune disease model** in Bcl-x(L) transgenic mice. Our data indicate that the passive cell death pathway is important in the pathogenesis of chronic EAE. These findings have implications for understanding the pathogenesis of **multiple sclerosis** and other autoimmune diseases.

L48 ANSWER 11 OF 24 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 3

2000077132 EMBASE Stem cell transplantation for treatment of severe autoimmune diseases: Current status and future perspectives. Jantunen E.; Myllykangas-Luosujarvi R.. Dr. E. Jantunen, Department of Medicine, Kuopio University Hospital, POB 1777, 70211 Kuopio, Finland. Bone Marrow Transplantation 25/4 (351-356) 2000.
Refs: 55.
ISSN: 0268-3369. CODEN: BMTRE. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Autoimmune diseases include a heterogenous group of disorders with

variable presentation and severity. Immunosuppressive and immunomodulatory therapies are often used for treatment with considerable success in some cases. These diseases may also be severe and refractory to conventional treatment. Thus more aggressive intervention might be indicated in a subset of patients. Animal studies suggest that high-dose therapy supported by stem cell transplantation may lead to remissions in experimental **autoimmune disease models**.
Anecdotal case reports suggest that the same may be the case in some human autoimmune diseases as well. This review attempts to summarise some current concepts and future perspectives on stem cell transplantation in the treatment of severe autoimmune diseases.

L48 ANSWER 12 OF 24 CAPLUS COPYRIGHT 2003 ACS
1999:96442 Document No. 130:167166 Methods for diagnosis and therapy of autoimmune disease, such as insulin dependent diabetes mellitus, involving retroviral superantigens. Conrad, Bernard; Mach, Bernard (Medigen S.A., Switz.). PCT Int. Appl. WO 9905527 A2 19990204, 165 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-EP4926 19980722.
AB The invention relates to a process for the diagnosis of a human autoimmune disease, including presymptomatic diagnosis, said human autoimmune disease being assocd. with human endogenous retrovirus (HERV) having Superantigen (SAg) activity. The methods comprise specifically detecting in a biol. sample of human origin at least one of the following: (I) the mRNA of an expressed human endogenous retrovirus having superantigen (SAg) activity, or fragments of such expressed retroviral mRNA, said retrovirus being assocd. with a given autoimmune disease, or (II) protein or peptide expressed by said retrovirus, or (III) antibodies specific to the protein expressed by said endogenous retrovirus, or (IV) SAg activity specifically assocd. with said endogenous retrovirus, detection of any of the species (I) to (IV) indicating presence of autoimmune disease or imminent onset of autoimmune disease.

L48 ANSWER 13 OF 24 CAPLUS COPYRIGHT 2003 ACS
1998:682518 Document No. 129:314989 Immune modulation by polypeptides related to soluble complement receptor CR1. Chernajovsky, Yuti; Annenkov, Alex (UK). PCT Int. Appl. WO 9845430 A1 19981015, 54 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-GB1012 19980406. PRIORITY: GB 1997-6950 19970405.
AB A sol. polypeptide which has a binding functionality of sol. complement receptor 1 (sCR1) towards C4b and C3b, e.g. a 95-kDa subsequence of CR1 (N-terminal 778 amino acid residues), can be used in the inhibition of a T-cell-mediated or a B-cell-mediated immune response in the context of an **autoimmune disease model**. This invention
points to a mechanism of action of sCR1 that is unpredicted from its known biochem. functions and indicates addnl. immune-modulatory functions of this mol. The invention further concerns prodn. of CR1-related polypeptides in-vivo, ex-vivo and in-vitro; their compns. and uses e.g. nucleic acid sequences encoding said polypeptides as DNA or RNA; recombinant nucleic acid vectors contg. such sequences; and cells expressing said polypeptides. The activity of sCR1 fragments can usefully

be assessed and measured by methods chosen from among, for example, inhibition of antigen-driven T-cell proliferative responses, of interferon-.gamma. secretion, and/or of antibody synthesis in the collagen-induced arthritis model; also usable is the reverse passive Arthus reaction in rat skin, analogous to an effect of full-length sCR1. Using a competitive ELISA to assess the protein concn. of sCR1, the 95-kDa mol. is 500-1000-fold more active than the full-length receptor.

L48 ANSWER 14 OF 24 CAPLUS COPYRIGHT 2003 ACS

1998:381854 Document No. 129:134882 Expression and characterization of recombinant soluble peptide: I-A complexes associated with murine experimental autoimmune diseases. Radu, Caius G.; Ober, Bertram T.; Colantonio, Lucia; Qadri, Ayub; Ward, E. Sally (Dep. Microbiol. Cancer Immunobiol. Cent., Univ. Texas Southwestern Med. Cent., Dallas, TX, 75235, USA). Journal of Immunology, 160(12), 5915-5921 (English) 1998. CODEN: JOIMA3. ISSN: 0022-1767. Publisher: American Association of Immunologists.

AB Structural and functional studies of murine MHC class II I-A mols. have been limited by the low yield and instability of sol., recombinant heterodimers. In the murine autoimmune diseases exptl. autoimmune encephalomyelitis and collagen-induced arthritis, MHC class II mols. I-Au and I-Aq present peptides derived from myelin basic protein and type II collagen, resp., to autoreactive T cells. To date, systems for the expression of these two I-A mols. in sol. form for use in structure-function relation studies have not been reported. In the present study, the authors have expressed functional I-Au and I-Aq mols. using a baculovirus insect cell system. The chain pairing and stability of the mols. were increased by covalently linking the antigenic peptides to .beta.-chains and adding carboxyl-terminal leucine zippers. Peptide:I-Aq complex quant. formed an SDS-stable dimer, whereas peptide:I-Au formed undetectable amts. However, the two complexes did not show any significant difference in their response to thermal denaturation as assessed by CD analyses. The autoantigen peptide:I-A complexes were highly active in stimulating cognate T cells to secrete IL-2 and inducing Ag-specific apoptosis of the T cells. Interestingly, the T cells were stimulated by these sol. mols. in the apparent absence of exptl. induced crosslinking of TCRs, indicating that they may have therapeutic potential in **autoimmune disease models**.

L48 ANSWER 15 OF 24 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 4

1999088259 EMBASE Expansion by self antigen is necessary for the induction of experimental autoimmune encephalomyelitis by T cells primed with a cross-reactive environmental antigen. Carrizosa A.M.; Nicholson L.B.; Farzan M.; Southwood S.; Sette A.; Sobel R.A.; Kuchroo V.K.. Dr. V.K. Kuchroo, Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School, 77 Louis Pasteur Ave., Boston, MA 02115, United States. kuchroo@cnd.bwh.harvard.edu. Journal of Immunology 161/7 (3307-3314) 1 Oct 1998.
Refs: 24.
ISSN: 0022-1767. CODEN: JOIMA3. Pub. Country: United States. Language: English. Summary Language: English.

AB Cross-reactivity with environmental antigens has been postulated as a mechanism responsible for the induction of autoimmune disease. Experimental autoimmune encephalomyelitis is a T cell-mediated **autoimmune disease model** inducible in susceptible strains of laboratory animals by immunization with protein constituents of myelin. We used myelin proteolipid protein (PLP) peptide 139-151 and its analogues to define motifs to search a protein database for structural homologues of PLP139-151 and identified five peptides derived from microbial Ags that elicit immune responses that cross- react with this self peptide. Exposure of naive SJL mice to the cross- reactive environmental peptides alone was insufficient to induce autoimmune disease even when animals were treated with Ag-nonspecific stimuli (superantigen

or LPS). However, immunization of SJL mice with suboptimal doses of PLP139-151 after priming with cross-reactive environmental peptides consistently induced experimental autoimmune encephalomyelitis. Furthermore, T cell lines from mice immunized with cross-reactive environmental peptides and restimulated in vitro with PLP139-151 could induce disease upon transfer into naive recipients. These data suggest that expansion by self Ag is required to break the threshold to autoimmune disease in animals primed with cross-reactive peptides.

L48 ANSWER 16 OF 24 SCISEARCH COPYRIGHT 2003 ISI (R)
97:882632 The Genuine Article (R) Number: YG657. Synergism between sirolimus and 1,25-dihydroxyvitamin D-3 in vitro and in vivo. Branisteanu D D; Mathieu C; Bouillon R (Reprint). UNIV CATHOLIQUE LOUVAIN, UZ GASTHUISBERG, LAB EXPT MED & ENDOCRINOL, HERESTR 49, B-3000 LOUVAIN, BELGIUM (Reprint); UNIV CATHOLIQUE LOUVAIN, UZ GASTHUISBERG, LAB EXPT MED & ENDOCRINOL, B-3000 LOUVAIN, BELGIUM; UNIV MED & PHARM, DEPT ENDOCRINOL, IASI 6600, ROMANIA. JOURNAL OF NEUROIMMUNOLOGY (NOV 1997) Vol. 79, No. 2, pp. 138-147 . Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0165-5728. Pub. country: BELGIUM; ROMANIA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The active form of vitamin D, 1 alpha,25-(OH)(2)D-3, displays immunomodulatory effects in vitro and in vivo at pharmacological levels. We evaluated the dose-effect relationship of 1,25(OH)(2)D-3 and sirolimus (rapamycin, RAP) in vitro, on the inhibition of PHA-srimulated PBMC proliferation, by using the median effect analysis. Pharmacological concentrations of 1,25(OH)(2)D-3 (between 10(-9) and 3 x 10(-6) M) interacted synergistically with RAP (combination index value of 0.01 for 50% suppression of PBMC proliferation). In vivo, the effect of 1,25(OH),D, and RAP combinations on the evolution of experimental allergic encephalomyelitis in SJL mice was analyzed. 1,25(OH)(2)D-3, given ip, in monotherapy, at a dose of 2 mu g/kg every two days, from day -3 until day +19 after disease induction, or RAP, injected daily at a dose of 0.3 mg/kg for the same period, decreased EAE incidence (paralysis in 70 and 55% of the animals, respectively, versus 98% in the placebo treated group, $p < 0.001$). The combination treatment using the two drugs in these subtherapeutical doses provided near-total clinical (8% paralysis, $p < 0.001$ compared to monotherapy with 1,25(OH),D, or RAP) and histological protection, comparable to that obtained with RAP in monotherapy at a threefold higher dose (1 mg/kg/d). When the two drugs were given using an alternate day administration schedule (RAP at 0.6 mg/kg and 1,25(OH)(2)D-3 at 2 mu g/kg. each given on alternate days from day -3 to 19), near total protection was again obtained (13% paralysis, $p < 0.001$ versus control). These in vitro and in vivo data support the existence of synergistic interactions between 1,25(OH)(2)D-3 and RAP. Considering the narrow therapeutic windows of both RAP and vitamin D-related compounds in **autoimmune disease models**, combinations of these drugs could find clinical application in reducing their individual therapeutically efficient doses to non-toxic levels. (C) 1997 Elsevier Science B.V.

L48 ANSWER 17 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
1996:36128 Document No.: PREV199698608263. Spontaneous inflammatory demyelinating disease in transgenic mice showing central nervous system-specific expression of tumor necrosis factor alpha. Probert, Lesley; Akassoglou, Katerina; Pasparakis, Manolis; Kontogeorgos, George; Kollias, George (1). (1) Dep. Mol. Genet., Hellenic Pasteur Inst., 127 Vas. Sofias Avenue, 115 21 Athens Greece. Proceedings of the National Academy of Sciences of the United States of America, (1995) Vol. 92, No. 24, pp. 11294-11298. ISSN: 0027-8424. Language: English.
AB Cytokines are now recognized to play important roles in the physiology of the central nervous system (CNS) during health and disease. Tumor necrosis factor alpha (TNF-alpha) has been implicated in the pathogenesis of

several human CNS disorders including **multiple sclerosis**, AIDS dementia, and cerebral malaria. We have generated transgenic mice that constitutively express a murine TNF-alpha transgene, under the control of its own promoter, specifically in their CNS and that spontaneously develop a chronic inflammatory demyelinating disease with 100% penetrance from around 3-8 weeks of age. High-level expression of the transgene was seen in neurons distributed throughout the brain. Disease is manifested by ataxia, seizures, and paresis and leads to early death. Histopathological analysis revealed infiltration of the meninges and CNS parenchyma by CD4+ and CD8+ T lymphocytes, widespread reactive astrocytosis and microgliosis, and focal demyelination. The direct action of TNF-alpha in the pathogenesis of this disease was confirmed by peripheral administration of a neutralizing anti-murine TNF-alpha antibody. This treatment completely prevented the development of neurological symptoms, T-cell infiltration into the CNS parenchyma, astrocytosis, and demyelination, and greatly reduced the severity of reactive microgliosis. These results demonstrate that overexpression of TNF-alpha in the CNS can cause abnormalities in nervous system structure and function. The disease induced in TNF-alpha transgenic mice shows clinical and histopathological features characteristic of inflammatory demyelinating CNS disorders in humans, and these mice represent a relevant in vivo model for their further study.

L48 ANSWER 18 OF 24 SCISEARCH COPYRIGHT 2003 ISI (R)

95:568556 The Genuine Article (R) Number: RQ080. SPREADING OF THE IMMUNE-RESPONSE TO DIFFERENT MYELIN BASIC-PROTEIN PEPTIDES IN CHRONIC EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS IN B10.RIII MICE. JANSSON L (Reprint); DIENER P; ENGSTROM A; OLSSON T; HOLMDAHL R. LUND UNIV, DEPT MED INFLAMAT RES, BOX 94, S-22100 LUND, SWEDEN (Reprint); HUDDINGE UNIV HOSP, KAROLINSKA INST, DEPT NEUROL, S-14186 HUDDINGE, SWEDEN; UNIV UPPSALA, DEPT MED & PHYSIOL CHEM, UPPSALA, SWEDEN; INST MED, MOLEC MED UNIT, STOCKHOLM, SWEDEN; KAROLINSKA HOSP, DEPT NEUROL, S-10401 STOCKHOLM, SWEDEN. EUROPEAN JOURNAL OF IMMUNOLOGY (AUG 1995) Vol. 25, No. 8, pp. 2195-2200. ISSN: 0014-2980. Pub. country: SWEDEN. Language: ENGLISH.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB B10.RIII mice develop chronic and relapsing experimental autoimmune encephalomyelitis (EAE) after immunization with the myelin basic protein (MBP) peptide 89-101 (VHFFKNIVTPRTP). To investigate the basis for the chronicity of the disease, the subsequent development of an immune responses to other parts of the MBP protein were investigated. Onset of disease occurs 9-25 days after immunization with MBPS9-101. T cell responses towards a series of MBP peptides were assessed in an enzyme-linked immunospot assay detecting single cells secreting IFN-gamma. There were responses not only to MBP89-101, but also towards peptides derived from sequences outside of MBP89-101. These peptides were of two kinds: those with sequences completely outside the 89-101 stretch of MBP; and those sharing a short sequence with MBP89-101 depending on alternative splicing of MBP mRNA. Immunization with these peptides also produced chronic EAE and a spreading of the immune response to other MBP peptides. Immunization with stepped peptides around the relevant region (MBP87-110) showed that peptides sharing a 6-amino-acid motif induced EAE after immunization. After MBP 89-101 peptide immunization, T cells isolated from lymph nodes did not cross-react in vitro to the other peptides sharing this motif. We suggest that one mechanism for the development of relapses during the disease course is the recruitment of new T cells with specificity for MBP peptides not derived from the peptide used for immunization. This is the first time such a mechanism has been demonstrated in a chronic **autoimmune disease model**.

L48 ANSWER 19 OF 24 CAPLUS COPYRIGHT 2003 ACS

1994:577011 Document No. 121:177011 **Autoimmune disease models** using SCID mice. Oshima, Shiro; Mima, Toru; Matsushita,

Masato; Saeki, Yukihiko (Osaka Univ., Suita, 565, Japan). Immunology Frontier, 4(4), 269-77 (Japanese) 1994. CODEN: IMFREG. ISSN: 0917-0774.

AB A review, with 21 refs., on severe combined immunodeficiency (SCID) mice, and reconstitution of human immune system by introduction of human peripheral blood mononuclear cells (PBMNC), fetal lymph tissue of liver and thymus, and bone marrow transplantation to SCID mice. Construction of model animals of autoimmune disease has been tried using SCID mice, using the introduction of patients' PBMNC of primary biliary cirrhosis, systemic lupus erythematosus, autoimmune thyroiditis, scleroderma and rheumatoid arthritis (RA), introduction of patients' thymic tissue of myasthenia gravis, and grafting of the target tissue of thyroid. The reconstruction of human diseases of **multiple sclerosis** and RA are described.

L48 ANSWER 20 OF 24 MEDLINE DUPLICATE 5

94351070 Document Number: 94351070. PubMed ID: 8071434. Estrogen induces a potent suppression of experimental autoimmune encephalomyelitis and collagen-induced arthritis in mice. Jansson L; Olsson T; Holmdahl R. (Department of Medical and Physiological Chemistry, Uppsala University, Sweden.) JOURNAL OF NEUROIMMUNOLOGY, (1994 Sep) 53 (2) 203-7. Journal code: 8109498. ISSN: 0165-5728. Pub. country: Netherlands. Language: English.

AB We have earlier described a chronic relapsing experimental autoimmune encephalomyelitis (EAE) in B10.RIII mice induced with a peptide of myelin basic protein (MBP), mimicking the course of **multiple sclerosis** in man. We now show that estrogens ameliorate chronic EAE. Castration of female mice led to an earlier disease onset (day 9 +/- 2 postimmunization (p.i.) in castrated mice vs. day 16 +/- 4 p.i. in normal mice). Long-term treatment with high levels of 17 beta-estradiol (E2) given as Silastic implants led to a dramatically delayed onset of disease in both castrated and normal female mice (mean onset day was day 39 +/- 14 and day 50 +/- 3, respectively). Treatment of castrated females by injections of E2, at a concentration which induces the serum levels seen at late stage pregnancy, delayed the onset approximately 1 week (mean onset 21 +/- 8). In contrast, treatment with estriol (E3), which was also given at doses corresponding to those levels seen during pregnancy, delayed the disease onset for a longer time (mean onset day 31 +/- 5). Five times higher doses of E2, compared with those seen during pregnancy, were required to obtain similar effects as the low E3 dose. The same mouse strain (B10.RIII) is also susceptible to induction of collagen-induced arthritis (CIA). We show here that also CIA is suppressed by the same treatments with E2 and E3, suggesting that similar estrogen-mediated mechanisms may operate to suppress these T-cell-dependent **autoimmune disease models**.

L48 ANSWER 21 OF 24 SCISEARCH COPYRIGHT 2003 ISI (R)

93:726929 The Genuine Article (R) Number: MK581. ENCEPHALITOGENIC TH1 CELLS ARE INHIBITED BY TH2 CELLS WITH RELATED PEPTIDE SPECIFICITY - RELATIVE ROLES OF INTERLEUKIN (IL)-4 AND IL-10. VANDERVEEN R C (Reprint); STOHLMAN S A. UNIV SO CALIF, SCH MED, DEPT NEUROL, MCH 142, 2025 ZONAL AVE, LOS ANGELES, CA, 90033 (Reprint); UNIV SO CALIF, SCH MED, DEPT MICROBIOL, LOS ANGELES, CA, 90033. JOURNAL OF NEUROIMMUNOLOGY (NOV/DEC 1993) Vol. 48, No. 2, pp. 213-220. ISSN: 0165-5728. Pub. country: USA. Language: ENGLISH. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Cytokines secreted by T-helper type 2 (Th2) cells inhibit the antigen-induced stimulation of type 1 (Th1) helper T cells. To study this form of regulation in an **autoimmune disease model**, the cytokines secreted by a Th2 clone specific for the encephalitogenic proteolipid protein (PLP) peptide 139-151 were tested for their ability to inhibit proliferation of an encephalitogenic Th1 clone specific for an epitope contained within the same peptide. Cytokines, produced by stimulation of the Th2 clone with CD3-specific monoclonal antibodies (mAbs), inhibited proliferation of the Th1 clone when

stimulated by antigen and splenic antigen-presenting cells (APC). Inhibition was, however, not antigen-specific since cytokines released upon stimulation of an unrelated Th2 clone were also inhibitory. Inhibition was found to be caused by effects on either antigen presentation or co-stimulatory activity of the APC and not by direct effects on the Th1 cells. MAbs for the two major regulatory Th2 cytokines were used to identify the inhibitory component secreted by activated Th2 cells. Interleukin-10 (IL-10)-specific mAb abolished the inhibitory effect, while mAb specific for IL-4 had no effect on inhibition. The addition of recombinant IL-4 (rIL-4) and rIL-10 confirmed that inhibition of Th1 proliferation was due to secretion of IL-10 by the Th2 clone and its subsequent effects on APC. The studies described here demonstrate that PLP-specific Th2 cells which recognize peptide 139-151 inhibit encephalitogenic Th1 cells which respond to an epitope on the same peptide. This phenomenon may be important for local, antigen-specific regulation of inflammation in the central nervous system.

L48 ANSWER 22 OF 24 SCISEARCH COPYRIGHT 2003 ISI (R)

92:485520 The Genuine Article (R) Number: JJ092. THE IMMUNOPATHOLOGY OF ACUTE EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS INDUCED WITH MYELIN PROTEOLIPID PROTEIN - T-CELL RECEPTORS IN INFLAMMATORY LESIONS. SOBEL R A (Reprint); KUCHROO V K. MASSACHUSETTS GEN HOSP, DEPT PATHOL, BOSTON, MA, 02114; EK SHRIVER CTR, DEPT BIOCHEM, WALTHAM, MA, 02254; HARVARD UNIV, SCH MED, DEPT PATHOL, BOSTON, MA, 02115. JOURNAL OF IMMUNOLOGY (15 AUG 1992) Vol. 149, No. 4, pp. 1444-1451. ISSN: 0022-1767. Pub. country: USA. Language: ENGLISH.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB To determine whether there is predominance of T cells expressing a particular TCR V-beta-chain in the inflammatory lesions of an **autoimmune disease model**, TCR expression was analyzed in central nervous system (CNS) tissues of mice with experimental allergic encephalomyelitis (EAE). Acute EAE was induced in SJL/J mice either by sensitization with a synthetic peptide corresponding to myelin proteolipid protein residues 139-151 or by adoptive transfer of myelin proteolipid protein peptide 139-151-specific encephalitogenic T cell clones. Mice were killed when they showed clinical signs of EAE or by 40 days after sensitization or T cell transfer. Cryostat CNS and lymphoid tissue sections were immunostained with a panel of mAb to T cell markers and proportions of stained cells were counted in inflammatory foci. In mice with both actively induced and adoptively transferred EAE, infiltrates consisted of many CD3+, TCR-alpha-beta+, and CD4+ cells, fewer CD8+ cells, and small numbers of TCR-gamma-delta+ cells. Approximately 30% of CD45+ leukocytes in the inflammatory foci were T cells. Cells expressing TCR V-beta 2, 3, 4, 6, 7 and 14 were detected in the infiltrates, whereas TCR V-beta-8 and 11, which that are deleted in SJL mice, were absent. When EAE was induced by transfer of T cell clones that use either V-beta 2, 6, 10, or 17, there was also a heterogeneous accumulation of T cells in the lesions. Similar proportions of TCR V-beta+ and gamma-delta+ cells were detected in EAE lesions and in the spleens of the mice. Thus, at the time that clinical signs are present in acute EAE, peripherally derived, heterogeneous TCR V-beta+ cells are found in CNS lesions, even when the immune response is initiated to a short peptide Ag or by a T cell clone using a single TCR V-beta.

L48 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2003 ACS

1992:488539 Document No. 117:88539 Spreading of T-cell autoimmunity to cryptic determinants of an autoantigen. Lehmann, Paul V.; Forsthuber, Thomas; Miller, Alexander; Sercarz, Eli E. (Dep. Microbiol. Mol. Genet., Univ. California, Los Angeles, CA, 90024, USA). Nature (London, United Kingdom), 358(6382), 155-7 (English) 1992. CODEN: NATUAS. ISSN: 0028-0836.

AB Immunization with myelin basic protein (MBP) induces exptl. allergic encephalomyelitis (EAE), a prototype of CD4+ T-cell mediated autoimmune

disease. In rodents, MBP-reactive T-cell clones are specific for a single, dominant determinant on MBP and use a highly restricted no. of T-cell receptor genes. Accordingly, EAE has been prevented by various receptor-specific treatments, suggesting similar strategies may be useful for therapy of human autoimmune disease. Here, in (SJL .times. B10.PL)F1 mice, immune dominance of a single determinant, MBP:Ac1-11, is confined to the inductive phase of EAE. In mice with chronic EAE, several addnl. determinants of MBP in peptides 35-47, 81-100 and 121-140 recall proliferative responses. Most importantly, reactivity to the latter determinants was also detected after induction of EAE with MBP peptide Ac1-11 alone; this demonstrates priming by endogenous MBP determinants. Thus, determinants of MBP that are cryptic after primary immunization can become immunogenic in the course of EAE. Diversification of the autoreactive T-cell repertoire due to determinant spreading has major implications for the pathogenesis of, and the therapeutic approach to, T-cell driven autoimmune disease.

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1991:128933 Document No.: BR40:60618. CHRONIC-RELAPSING EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS IN LEWIS RATS CORRELATION BETWEEN CLINICAL STATE AND ANTIMYELIN BASIC PROTEIN REACTIVITY IN DRAINING LYMPH NODE CELLS. CHABANNES D; BOREL J-F. PRECLIN. RES., SANDOZ PHARMA LTD., 4002 BASEL, SWITZ.. EIGHTH INTERNATIONAL WORKSHOP ON ALLOANTIGENIC SYSTEMS IN THE RAT, CESKE BUDEJOVICE, CZECHOSLOVAKIA, APRIL 23-26, 1990. TRANSPLANT PROC. (1990) 22 (6), 2591-2593. CODEN: TRPPA8. ISSN: 0041-1345. Language: English.

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